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SEARCH REQUEST FORM

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Requester's Full Name: R Gitomer Examiner #: 69630 Date: 12/3/02

Art Unit: 1651 Phone Number 308-0732 Serial Number: 10/050,441

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

Earliest Priority Filing Date: _____

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

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Searcher Phone #: 4468	AA Sequence (#)		Dialog	
Searcher Location:	Structure (#)		Questel/Orbit	
Date Searcher Picked Up: 12/4/02	Bibliographic	✓	Dr.Link	
Date Completed: 12/4/02	Litigation		Lexis/Nexis	
Searcher Prep & Review Time:	Fulltext		Sequence Systems	
Clerical Prep Time: 15	Patent Family		WWW/Internet	
Online Time: + 120	Other		Other (specify)	

PTO-1590 (8-01)

Jan Delaval
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L2             2 S E4,E17
L3             1 S CALCIUM/CN
L4             1 S MAGNESIUM/CN
               E BLOOD-COAGULATION FACTOR/CN
               E BLOOD-COAGULATION FACTOR IXA/CN
L5             1 S E3
               E BLOOD-COAGULATION FACTOR XIA/CN
L6             1 S E3
               E BLOOD-COAGULATION FACTOR XIIA/CN
L7             1 S E3
               E NATIVE HUMAN TISSUE FACTOR/CN
               E HUMAN TISSUE FACTOR/CN
               E TISSUE FACTOR/CN
L8             1 S E4
               E RECOMBINANT TISSUE FACTOR/CN
               E RECOMBINANT HUMAN TISSUE FACTOR/CN
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               E BLOOD-COAGULATION FACTOR VIIA/CN
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               E RECOMBINANT BLOOD-COAGULATION FACTOR VIIA/CN
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               E PROTEIN C/CN
L11            1 S E3
               E ACTIVATED PROTEIN C/CN
L12            1 S E3
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L14            1 S E3
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L16           65 S E3
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               E BLOOD-COAGULATION FACTOR VIII/CN
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               E BLOOD-COAGULATION FACTOR IX/CN
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               E BLOOD-COAGULATION FACTOR X/CN
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L22            1 S E3
               E PROTEIN C ACTIVATING SNAKE VENOM/CN
               E THROMBIN/CN
L23            1 S E3
               E THROMBOMODULIN/CN
L24            1 S E3
               E PROTEIN C ACTIVATOR/CN
L25            1 S E3
               E RECOMBINANT PROTEIN C ACTIVATOR/CN
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L26        13488 S L1
L27       296092 S L3
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L29       436328 S L26-L28
L30         9917 S L2
L31       164242 S L4
L32       134977 S MG2 OR (MG OR MAGNESIUM)(L)ION
L33       127612 S L30-L32 AND L29
L34           43 S L33 AND PROTEIN C
L35           14 S L33 AND L11,L12

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L40           278 S L33 AND L5-L10,L14-L25
L41            12 S L38,L39 AND L40
L42             6 S L38,L39,L41 AND (BIOCHEM?(L)METHOD?)/SC,SX
L43             1 S L38,L39,L41 AND (SNAKE(L)VENOM?)
                  E BLOOD ANALYSIS/CT
                  E E3+ALL
L44        112205 S E3,E2+NT
L45           930 S L33 AND L44
L46            12 S L45 AND L40
L47             3 S L45 AND L38,L39,L41-L43
L48          4370 S C REACT? PROTEIN
L49            15 S L48 AND L33
L50            63 S L49,L46,L47,L38,L39,L41-L43
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                  E ROSEIN B/AU
                  E ROSEN B/AU
L52           128 S E3,E32
                  E HALL C/AU
L53           281 S E3,E27
                  E HALL CHRIS/AU
L54            18 S E3
L55            12 S E10-E12
L56             2 S L52-L55 AND L33
L57             1 S L56 NOT ADENOSINE/TI
L58            22 S L51,L57
                  SAV L58 GITOMER050/A


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FILE COVERS 1907 - 11 Dec 2002 VOL 137 ISS 24
FILE LAST UPDATED: 10 Dec 2002 (20021210/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

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L123 ANSWER 1 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN **2002:588931** HCAPLUS
DN **137:106098**
TI Method for predicting the presence of haemostatic dysfunction in a patient sample
IN Toh, Cheng Hock; Downey, Colin; Fischer, Timothy J.
PA Biomerieux, USA
SO U.S., 41 pp., Cont.-in-part of U.S. Ser. No. 244,340.
CODEN: USXXAM
DT Patent
LA English
IC ICM G01N033-86
NCL 436069000
CC **9-16** (**Biochemical Methods**)
Section cross-reference(s): 1, 14
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6429017	B1	20020806	US 1999-372954	19990812
	WO 2001013125	A1	20010222	WO 2000-US21022	20000802
	W: AU, CA, JP, KR, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 1200837	A1	20020502	EP 2000-953788	20000802
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
PRAI	US 1999-244340	A2	19990204		
	US 1999-372954	A2	19990812		
	WO 2000-US21022	W	20000802		

AB A method which may be used to det. haemostatic dysfunction in a patient is carried out by (a) adding a reagent to a test sample, wherein the test sample includes at least a component of a blood sample from a patient; and then (b) measuring the formation of a ppt. due to the reaction of the test sample and the reagent, over time so as to derive a time-dependent measurement profile, the reagent forming a ppt. in the test sample without causing substantial fibrin polymn.
ST haemostatic dysfunction detn blood coagulation
IT **Proteins**
RL: ANT (Analyte); ANST (Analytical study)
(**C**-reactive; method for predicting presence of hemostatic dysfunction in a patient sample)
IT Proteins
RL: ANT (Analyte); ANST (Analytical study)
(SAA (serum amyloid A); method for predicting presence of hemostatic dysfunction in a patient sample)
IT **Blood coagulation**
(disseminated intravascular; method for predicting presence of

hemostatic dysfunction in a patient sample)

IT Antibiotics
Blood
Blood analysis
Blood coagulation
Blood plasma
Blood transfusion
Hemorrhage
Immunoassay
Precipitation (chemical)
Thrombosis
UV and visible spectroscopy
(method for predicting presence of hemostatic dysfunction in a patient sample)

IT Metals, uses
Transition metals, uses
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(method for predicting presence of hemostatic dysfunction in a patient sample)

IT Fibrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method for predicting presence of hemostatic dysfunction in a patient sample)

IT **Blood-coagulation factors**
Interleukin 1
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for predicting presence of hemostatic dysfunction in a patient sample)

IT **9001-26-7**, Prothrombin
RL: ANT (Analyte); ANST (Analytical study)
(method for predicting presence of hemostatic dysfunction in a patient sample)

IT 7439-89-6, Iron, uses **7439-95-4**, **Magnesium**, uses 7439-96-5, Manganese, uses 7440-39-3, Barium, uses **7440-70-2**, **Calcium**, uses
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(method for predicting presence of hemostatic dysfunction in a patient sample)

IT 8001-27-2, Hirudin 9000-94-6, Antithrombin 9005-49-6, Heparin, biological studies 71142-71-7, PPACK 93050-91-0, I2581
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(method for predicting presence of hemostatic dysfunction in a patient sample)

IT 57-13-6, Urea, analysis 60-00-4, EDTA, analysis 288-32-4, Imidazole, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(method for predicting presence of hemostatic dysfunction in a patient sample)

RE.CNT 185 THERE ARE 185 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Anderson; US 5221628 A 1993 HCAPLUS
(2) Anon; FR 2364453 1976
(3) Anon; SU 590665 1976
(4) Anon; DE 2635081 1978
(5) Anon; GB 2005014 1979
(6) Anon; EP 0115459 1984 HCAPLUS
(7) Anon; SU 1076086 1984
(8) Anon; JP 59203959 1984
(9) Anon; DE 3502878 1985 HCAPLUS
(10) Anon; JP 60114768 1985
(11) Anon; JP 61272655 1986

(12) Anon; WO 8606840 1986 HCAPLUS
(13) Anon; SU 1691741 1989
(14) Anon; WO 8909628 1989 HCAPLUS
(15) Anon; SU 1777089 1990 HCAPLUS
(16) Anon; EP 0434377 1991 HCAPLUS
(17) Anon; JP 05180835 1991 HCAPLUS
(18) Anon; RU 2012877 1991
(19) Anon; WO 9100872 1991 HCAPLUS
(20) Anon; WO 9101383 1991 HCAPLUS
(21) Anon; WO 9101497 1991 HCAPLUS
(22) Anon; WO 9102812 1991 HCAPLUS
(23) Anon; WO 9105874 1991
(24) Anon; WO 9108460 1991 HCAPLUS
(25) Anon; WO 9116453 1991 HCAPLUS
(26) Anon; JP 04254760 1992 HCAPLUS
(27) Anon; JP 06027115 1992
(28) Anon; EP 0525273 1993
(29) Anon; WO 9307491 1993 HCAPLUS
(30) Anon; WO 9309438 1993 HCAPLUS
(31) Anon; WO 9324530 1993 HCAPLUS
(32) Anon; JP 06249855 1994 HCAPLUS
(33) Anon; WO 9407145 1994 HCAPLUS
(34) Anon; WO 9411714 1994
(35) Anon; WO 9416095 1994
(36) Anon; WO 9505590 1995 HCAPLUS
(37) Anon; WO 9508121 1995 HCAPLUS
(38) Anon; WO 9530154 1995 HCAPLUS
(39) Anon; WO 9642018 1995 HCAPLUS
(40) Anon; JP 10104239 1996 HCAPLUS
(41) Anon; RU 2061953 1996 HCAPLUS
(42) Anon; RU 2070327 1996 HCAPLUS
(43) Anon; WO 9606624 1996 HCAPLUS
(44) Anon; WO 9614581 1996 HCAPLUS
(45) Anon; WO 9621740 1996 HCAPLUS
(46) Anon; WO 9641291 1996
(47) Anon; WO 9704317 1997 HCAPLUS
(48) Anon; WO 9720066 1997 HCAPLUS
(49) Anon; WO 9734698 1997
(50) Anon; EP 818680 1998 HCAPLUS
(51) Anon; EP 841566 1998 HCAPLUS
(52) Anon; WO 9809628 1998 HCAPLUS
(53) Anon; WO 9934208 1999 HCAPLUS
(54) Anon; WO 9947699 1999 HCAPLUS
(55) Anon; WO PCTUS0021022 2001
(56) Anon; 3 .times. 15 Test Kit for Detection of Plasma Protein C Activity Using a Clotting End-Point, Product # ACC-45 1989, P1
(57) Anon; Atherotech-VAP/CAD Lipoprotein Risk Assessment Test, Sample of VAP Profile
(58) Anon; Ortho Factor VIII: C Deficient Plasma 1998, P1
(59) Anon; Package insert for Ortho Brain Thromboplastic Reagent 1985, P1
(60) Astion; Arch Pathol Lab Med 1992, V116, P995 MEDLINE
(61) Astion; Clin Chem 1993, V39(9), P1998 MEDLINE
(62) Bacus; US 4199748 A 1980
(63) Baugh; US 6010911 A 2000
(64) Baughman; US 4289498 A 1981 HCAPLUS
(65) Baum; Neural Computation 1989, P81
(66) Baumann; Haemostasis 1989, V19, P309 HCAPLUS
(67) Baumann; Haemostasis 1991, V21, P329 HCAPLUS
(68) Bennett; US 4902630 A 1990 HCAPLUS
(69) Bluestein; Nurse Practitioner 1991, V16(7), P39 MEDLINE
(70) Boone; Investigative Radiology 1990, V25(9), P1013
(71) Brandt; Arch Pathol Lab Med 1991, V115, P109 MEDLINE
(72) Braun; Coagulation Methods Instrumentation and Quality Control, Abstract

#1286 1995, P1236
(73) Braun; Thromb Haemost 1997, V78, P1079 HCAPLUS
(74) Cabana; J Immunol 1982, V128(5), P2342 HCAPLUS
(75) Cabana; J Immunol 1983, V130(4), P1736 HCAPLUS
(76) Cabana; J Lipid Res 1989, V30(1), P39 HCAPLUS
(77) Cabana; Journal of Lipid Research 1989, V30, P39 HCAPLUS
(78) Canivet; Acta Anaesthesiologica Belgica 1989, V40(4)
(79) Carrol; The Clot Signature and New Aspects in Coagulation Testing 1989, P1
(80) Carroll; US 5169786 A 1992 HCAPLUS
(81) Carroll; US 5981285 A 1999 HCAPLUS
(82) Chang; US 5473732 A 1995
(83) Christner; J Biol Chem 1994, V269(13), P9760 HCAPLUS
(84) Collins; US 5526111 A 1996
(85) Dassen; J Electrocardiol 1990, V23(Suppl), P200
(86) de Beer; J Exp Med 1982, V156(1), P230 HCAPLUS
(87) Dennis; Utility of Prothrombin Time Waveform Analysis in the Routine Clinical Setting, 1999
(88) Diamond; US 5567596 A 1996 HCAPLUS
(89) Downey; British Journal of Haematology 1997, V97, P000
(90) Downey; International Journal of Hematology, Abstracts of the 26th Congress of the International Society of Haematology 1996
(91) Downey; The Robustness and Reproducibility of APIT Waveform Analysis in Relation to Reagent and Batch Variation,
(92) Downey, C; Br J Haematol 1997, V136, P18854
(93) Eichelberger; US 4047890 A 1977 HCAPLUS
(94) Eitoku; Physico Chem Biol 1993, V37(1), P19 HCAPLUS
(95) Engler, R; CR Seances Soc Biol Fil 1995, V189(4), P563 HCAPLUS
(96) Faupel; US 5715821 A 1998
(97) Fischer; US 5646046 A 1997
(98) Furlong; Am J Clin Pathol 1991, V96(1), P134 MEDLINE
(99) Gavin; US 5591403 A 1997 HCAPLUS
(100) Gewurz; Advances in Internal Medicine 1982, V27, P345 HCAPLUS
(101) Givens; US 5708591 A 1998
(102) Givens; US 6101449 A 2000 HCAPLUS
(103) Givens; US 6269313 B1 2001
(104) Givens; Clin Chem, Abstract #399 1996, V42(6), PS192
(105) Givens; Comput Biol Med 1996, V26(6), P463 HCAPLUS
(106) Givens; Int J Med Inf 1997, V46, P129 MEDLINE
(107) Givens, T; Clin Hemostasis Rev 1997, P11
(108) Griffin; US 5705395 A 1998 HCAPLUS
(109) Griffin; US 5834223 A 1998 HCAPLUS
(110) Gross; US 3458287 A 1969
(111) Grossman; US 5156974 A 1992 HCAPLUS
(112) Ham; US 5553616 A 1996
(113) Harris; Clin Res 1989, V37(2), P614A
(114) Hassouna; US 5525477 A 1996 HCAPLUS
(115) Heuck; Haemostasis 1991, V21, P10 HCAPLUS
(116) Hoffman; Interface (Organon Teknika) 1990, P3 MEDLINE
(117) Hulman; Clinica Chimica Acta 1987, V165, P89 HCAPLUS
(118) Hulman; The Lancet 1982, P1426 HCAPLUS
(119) Hulman, G; Journal of Pathology 1995, V176, P3 MEDLINE
(120) Husebekk; Scan J Immunol 1988, V28, P653 HCAPLUS
(121) Husebekk; Scan J Immunol 1988, V28, P653 HCAPLUS
(122) Kane; US 3658480 A 1972
(123) Khanin; J Theor Biol 1989, V136, P127 HCAPLUS
(124) Lagrand; Circulation 1999, P96 MEDLINE
(125) Lindh; Critical Care Medicine 1985, V13(3), P151 MEDLINE
(126) Malle; Atherosclerosis 1993, V102, P131 HCAPLUS
(127) Mann; US 5856114 A 1999 HCAPLUS
(128) Matschiner; US 5716795 A 1998 HCAPLUS
(129) Maury, C; Marker Proteins in Inflammation Proceedings, Symposium 1985, V3
(130) McCarty; Laboratory of Bacteriology and Immunology 1982, V389, P1 HCAPLUS
(131) McDonald; J Immunol Methods 1991, V144(2), P149 HCAPLUS

(132) Merritt; US 5003065 A 1991 HCAPLUS
(133) Meyer; US 5218529 A 1993
(134) Miyashita; US 4766083 A 1988 HCAPLUS
(135) Nozaki; US 5563983 A 1996
(136) Oberhardt; US 5670329 A 1997 HCAPLUS
(137) Owen; US 3307392 A 1967
(138) Pattichis; Med Biol Eng Comput 1995, V33(3), P499
(139) Pepys; Int Rev Exp Pathol 1985, V27, P83 HCAPLUS
(140) Pohl; Haemostasis 1994, V24, P325 MEDLINE
(141) Potempa; US 5593897 A 1997 HCAPLUS
(142) Proksch; US 5055412 A 1991 HCAPLUS
(143) Ravdin; US 5862304 A 1999
(144) Richter; Clinica Chimica Acta 1997, V261, P141 HCAPLUS
(145) Ridker; US 6040147 A 2000 HCAPLUS
(146) Robin; Intensive Care Med 1999, V25(Supplement 1), PS63
(147) Rowe; Clin Exp Immunol V58(1), P245 HCAPLUS
(148) Rowe; Clin Exp Immunol 1984, 58, P237
(149) Rowe; Clin Exp Immunol 1986, 66, P241
(150) Rowe; J Exp Med 1984, V159, P604 HCAPLUS
(151) Rutenberg; US 4965725 A 1990
(152) Rybarska; Journal Physiology and Pharmacology 1995, V46(2), P221 HCAPLUS
(153) Sabbatini, R; Conf of the Engineering in Medicine and Biology Society 1983, V15, P265
(154) Saito; US 4217107 A 1980
(155) Saito; US 4279616 A 1981 HCAPLUS
(156) Sammalkorpi; Annals of Medicine 1990, V22, P397 MEDLINE
(157) Sato; US 5473551 A 1995 HCAPLUS
(158) Schwalbe; Biochemistry 1995, V34(33), P10432 HCAPLUS
(159) Schweiger; Clin Chem 1993, V39(9), P1966 MEDLINE
(160) Selker; US 4998535 A 1991
(161) Serban; US 4782014 A 1988 HCAPLUS
(162) Simmons, A; Technical Hematology (Third Edition), P334
(163) Simons; US 4040788 A 1977
(164) Soe; US 5500345 A 1996 HCAPLUS
(165) Stewart; Sensitive and Rapid Measurement of C-Reactive Protein (CRP) by Lipid Agglutination, 1986, P585
(166) Swanson; Biochem Biophys Acta 1992, V1160(3), P309 HCAPLUS
(167) Sweeney; Blood, Abstract #1509 1989, V74(Suppl 17), P395
(168) Sweeney; Blood, Abstract #1745 1990, V76(Suppl 110), P439a
(169) Sweeney; The American Society of Hematology Abstract Reproduction Form 1989
(170) Swets, J; Science 1988, V240, P1285 MEDLINE
(171) Talstad, I; Haemostasis 1993, V23, P19 MEDLINE
(172) Toh; 5th World Congress on Trauma, Shock, Inflammation and Sepis-Pathophysiology, Immune Consequences and Therapy 2000
(173) Toh; Characterisation of the Novel Calcium-Activation, Thrombin Suppression Assay (CaTs) in the DIC of Sepsis,
(174) Toh; Clinical Hemostasis Review 1998
(175) Toh; Draft Preview of Abstract #450426 1999
(176) Toh; The Mechanism Underlying the Atypical Clot Waveform Profile of DIC is Thrombin-independent but Calcium-dependent, 2000
(177) Toh; XVIIth Congress International Society for Thrombosis & Haemostasis 1999
(178) Toh; XVIIth Congress International Society for Thrombosis & Haemostasis 1999
(179) Toh; XVIIth Congress International Society for Thrombosis & Haemostasis 1999
(180) Triplett; Graphic monitoring of coagulation assays 1989, P1
(181) Wilkins; Clin Chem, Part 1 1994, V40(7), P1284 HCAPLUS
(182) Wu; US 5358852 A 1994 HCAPLUS
(183) Yonekawa; US 5388164 A 1995
(184) Zuckerman; Thromb Haemostas 1981, V46, P752 MEDLINE
(185) Zweig; Clin Chem 1993, V39(4), P561 HCAPLUS

L123 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN **2001:228352** HCAPLUS
DN **134:249240**
TI Method and constituent for processing blood for determining blood cell reaction
IN Nagai, Hiroyuki
PA Asahi Chemical Industry Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 10 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM G01N033-48
ICS G01N033-48; A61B005-15
CC **9-16** (Biochemical Methods)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001083144	A2	20010330	JP 1999-256245	19990909

PI JP 2001083144 A2 20010330 JP 1999-256245 19990909

AB A method is provided for processing blood so as to det. a blood cell reaction (e.g., mediator sepn. reaction from blood cell) with an excellent reproducibility and a low cost without sepg. the blood cell. The blood cell reaction is performed upon adding to a blood sample a chelating agent (e.g., EDTA, citric acid, oxalic acid), an anticoagulant without a chelating ability (e.g., heparin, plasmin, proteinase, azo dye, hirudin, dicumarol, thrombomodulin, antibody to anticoagulant, anticoagulant-binding receptor) and a **metal** salt (e.g., chloride, sulfate, carbonate, nitrate, phosphate) capable of eluting a **divalent cation** (e.g., **Ca2+**, **Mg2+**, Mn2+, Zn2+, Cd2+, Cu2+) in an aq. medium. A reagent constituent used for this method is also claimed. The sepn. reaction of an mediator (e.g, histamine, leukotriene, platelet activating factor, cytokine) from blood cell was detd. with an excellent reproducibility using blood samples processed by this method.

ST chelating agent anticoagulant metal blood analysis; blood cell mediator hystamine leukotriene cytokine

IT Receptors
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(anticoagulant-binding; method and constituent for processing blood for detg. blood cell reaction)

IT **Cations**
(**divalent**; method and constituent for processing blood for detg. blood cell reaction)

IT Anticoagulants
Azo dyes
Blood
Blood analysis
Blood cell
Chelating agents
Sample preparation
(method and constituent for processing blood for detg. blood cell reaction)

IT Cytokines
Leukotrienes
RL: ANT (Analyte); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell reaction)

IT Carbonates, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell reaction)

IT Chlorides, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)

(method and constituent for processing blood for detg. blood cell reaction)

IT Nitrates, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell reaction)

IT Phosphates, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell reaction)

IT Sulfates, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell reaction)

IT **Thrombomodulin**
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell reaction)

IT Antibodies
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(to anticoagulant; method and constituent for processing blood for detg. blood cell reaction)

IT 51-45-6, Histamine, analysis 65154-06-5, Platelet-activating factor
RL: ANT (Analyte); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell reaction)

IT 643-79-8, o-Phthalaldehyde
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(method and constituent for processing blood for detg. blood cell reaction)

IT 60-00-4, EDTA, analysis 77-92-9, Citric acid, analysis 139-33-3 144-62-7, Oxalic acid, analysis 471-34-1, **Calcium** carbonate, analysis **7439-95-4, Magnesium**, analysis 7439-96-5, Manganese, analysis 7440-43-9, Cadmium, analysis 7440-50-8, Copper, analysis 7440-66-6, Zinc, analysis **7440-70-2, Calcium**, analysis 7773-01-5, Manganese chloride 7778-18-9, **Calcium** sulfate 7786-30-3, **Magnesium** chloride, analysis 8001-27-2, Hirudin 9001-90-5, Plasmin 9001-92-7, Proteinase **9002-04-4**, Thrombin 9005-49-6, Heparin, analysis 9041-08-1, Sodium heparin 10043-52-4, **Calcium** chloride, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(method and constituent for processing blood for detg. blood cell reaction)

L123 ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN **2001:137491** HCAPLUS
DN **134:159904**
TI A method for predicting the presence of haemostatic dysfunction in a patient sample
IN Toh, Cheng Hok; Downey, Colin; Fischer, Timothy J.
PA Akzo Nobel N.V., Neth.
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM G01N033-86
CC **9-16** (Biochemical Methods)
Section cross-reference(s): 1, 14
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001013125	A1	20010222	WO 2000-US21022	20000802
	W: AU, CA, JP, KR, US				

RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
US 6429017 B1 20020806 US 1999-372954 19990812
EP 1200837 A1 20020502 EP 2000-953788 20000802
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY
PRAI US 1999-372954 A2 19990812
US 1999-244340 A2 19990204
WO 2000-US21022 W 20000802

AB Disclosed is a method for detecting a ppt. in a test sample in the absence of clot formation. The ppt. detection allows for the prediction haemostatic dysfunction in patients, which can lead to bleeding or thrombosis or particularly to Disseminated Intravascular Coagulation (DIC).

ST haemostatic dysfunction detn blood coagulation

IT Proteins, specific or class
RL: ANT (Analyte); ANST (Analytical study)
(C-reactive; method for predicting presence of hemostatic dysfunction in a patient sample)

IT Proteins, specific or class
RL: ANT (Analyte); ANST (Analytical study)
(SAA (serum amyloid A); method for predicting presence of hemostatic dysfunction in a patient sample)

IT **Blood coagulation**
(disseminated intravascular; method for predicting presence of hemostatic dysfunction in a patient sample)

IT Antibiotics
Blood
Blood analysis
Blood coagulation
Blood plasma
Blood transfusion
Hemorrhage
Immunoassay
Precipitation (chemical)
Thrombosis
UV and visible spectroscopy
(method for predicting presence of hemostatic dysfunction in a patient sample)

IT Metals, uses
Transition metals, uses
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(method for predicting presence of hemostatic dysfunction in a patient sample)

IT **Blood-coagulation factors**
Interleukin 1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for predicting presence of hemostatic dysfunction in a patient sample)

IT Fibrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method for predicting presence of hemostatic dysfunction in a patient sample)

IT **9001-26-7**, Prothrombin
RL: ANT (Analyte); ANST (Analytical study)
(method for predicting presence of hemostatic dysfunction in a patient sample)

IT 7439-89-6, Iron, uses **7439-95-4, Magnesium**, uses
7439-96-5, Manganese, uses 7440-39-3, Barium, uses **7440-70-2, Calcium**, uses
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)

(method for predicting presence of hemostatic dysfunction in a patient sample)

IT 8001-27-2, Hirudin 9000-94-6, Antithrombin 9005-49-6, Heparin, biological studies 71142-71-7, PPACK 93050-91-0, I2581
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(method for predicting presence of hemostatic dysfunction in a patient sample)

IT 57-13-6, Urea, analysis 60-00-4, EDTA, analysis 288-32-4, Imidazole, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(method for predicting presence of hemostatic dysfunction in a patient sample)

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Braun; WO 9934208 A 1999 HCAPLUS
(2) Downey, C; British Journal of Haematology 1997, V97(000-000), P1
(3) Givens; US 5708591 A 1998
(4) Proksch; US 5055412 A 1991 HCAPLUS
(5) Rosen; WO 9947699 A 1999 HCAPLUS
(6) Toh; A Previously Unrecognised Mechanism that is Calcium-Dependent and Thrombin-Independent Characterises the Pre-DIC State, abstract no 450426 1999
(7) Toh, C; 5th World Congress on TRAUMA, SHOCK, INFLAMMATION AND SEPSIS-Pathophysiology, Immune Consequences and Therapy 2000
(8) Toh, C; The Mechanism Underlying the Atypical Clot Waveform Profile of DIC Is Thrombin-Independent but Calcium-Dependent 2000

L123 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN **2000:741093** HCAPLUS
DN **133:263563**
TI A global test for evaluating the functionality of the thrombin/antithrombin system
IN Preda, Luigi
PA Instrumentation Laboratory S.p.A., Italy
SO Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM G01N033-86
ICS C12Q001-56
CC **9-16** (Biochemical Methods)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1045250	A1	20001018	EP 1999-830209	19990412
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	CA 2305085	AA	20001012	CA 2000-2305085	20000412
	JP 2000329770	A2	20001130	JP 2000-110639	20000412
PRAI	EP 1999-830209	A	19990412		

AB The present invention relates to an anal. test for evaluating the functionality of the thrombin/antithrombin system. In particular, the present invention relates to an anal. method for evaluating the functionality of the thrombin/antithrombin system, comprising the following steps: (a) mixing a sample of plasma to be analyzed with an agent promoting the inhibitory activity of antithrombin; (b) adding a Factor II activating agent to the mixt. produced in step (a); (c) measuring the time taken to convert the fibrinogen of the mixt. produced in step (b) into fibrin.

ST global test thrombin antithrombin system

IT **Blood analysis**

Blood plasma
Buffers
Echis carinatus
Freeze drying
Mathematical methods
Mixing
Test kits
Venoms
(a global test for evaluating functionality of thrombin/antithrombin system)

IT Fibrinogens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(a global test for evaluating functionality of thrombin/antithrombin system)

IT Fibrins
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(a global test for evaluating functionality of thrombin/antithrombin system)

IT 9000-94-6, Antithrombin **9002-04-4**, Thrombin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(a global test for evaluating functionality of thrombin/antithrombin system)

IT 9005-49-6, Heparin, biological studies 9041-08-1, Sodium heparin 9045-22-1, Lithium heparin **14127-61-8D**, Calciumion, salts, biological studies 17341-25-2D, Sodiumion, salts, biological studies **22537-22-0D**, **Mg2+**, salts, biological studies 24203-36-9D, salts, biological studies 24967-94-0, Dermatan sulphate 37270-89-6, **Calcium** heparin
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(a global test for evaluating functionality of thrombin/antithrombin system)

IT **9001-26-7**, Blood-coagulation factor II
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(activating agent; a global test for evaluating functionality of thrombin/antithrombin system)

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Baxter Diagnostics Inc; WO 9207954 A 1992 HCAPLUS
(2) Eisai Co Ltd; EP 0814155 A 1997 HCAPLUS
(3) Karges, H; US 4106990 A 1978
(4) Matschiner, J; US 5716795 A 1998 HCAPLUS
(5) Nowak, G; Seminars in Thrombosis and Hemostasis, STN Database accession no 96401341 1996, V22(2), P197 MEDLINE
(6) Preda, L; US 5780255 A 1998 HCAPLUS
(7) S E M S; GB 1157593 A 1969 HCAPLUS
(8) Univ Nebraska; WO 9307491 A 1993 HCAPLUS

L123 ANSWER 5 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN **1999:614172** HCAPLUS
DN **131:225815**
TI Screening for blood coagulation defects using metal ions
IN **Rosen, Bert Steffen; Hall, Christina Maria Yvonne**
PA Chromogenix AB, Swed.
SO PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12Q001-56
ICS G01N033-86
CC **9-5 (Biochemical Methods)**

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9947699	A1	19990923	WO 1999-EP1599	19990311
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 947585	A1	19991006	EP 1998-105043	19980319
	EP 947585	B1	20010725		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	AT 203567	E	20010815	AT 1998-105043	19980319
	ES 2162361	T3	20011216	ES 1998-105043	19980319
	CA 2334935	AA	19990923	CA 1999-2334935	19990311
	AU 9930339	A1	19991011	AU 1999-30339	19990311
	US 6395501	B1	20020528	US 1999-273413	19990319
	US 2002115127	A1	20020822	US 2002-50441	20020116
PRAI	EP 1998-105043	A	19980319		
	WO 1999-EP1599	W	19990311		
	US 1999-273413	A1	19990319		

AB An in vitro photometric method for qual. screening and quant. detn. of the functional activity of components of the **Protein C** anticoagulant pathway of blood coagulation, comprising measuring the conversion rate of an exogenous substrate by an enzyme, the activity of which is related to the **Protein C** anticoagulant activity, in a blood sample of a human comprising coagulation factors and said exogenous substrate after at least partial activation of coagulation through the intrinsic, extrinsic or common pathway and triggering coagulation by adding **calcium ions**; and comparing said conversion rate with the conversion rate of a normal human blood sample detd. in the same way, comprises adding further metal(s) **ions** to said sample. Kits and reagents for use in the method are also disclosed. By including manganese and **magnesium ions** with the **calcium ions** in a reaction system for the detn. of **Protein C** activity, a strong enhancement of the anticoagulant activity was obtained.

ST blood coagulation defect screening metal **ion; protein C** blood assay manganese **magnesium ion**

IT Chromophores
Fluorescent substances
Luminescent substances
(as leaving group on enzyme substrate; screening for blood coagulation defects using metal ions)

IT **Metals, biological studies**
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**divalent** ions; screening for blood coagulation defects using **metal** ions)

IT Brain
Egg yolk
Placenta
Platelet (blood)
Soybean (Glycine max)
(phospholipids of; screening for blood coagulation defects using metal ions)

IT Fibrins
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical

study); BIOL (Biological study); PROC (Process); USES (Uses)
(polymn. inhibitor; screening for blood coagulation defects using metal ions)

IT **Blood-coagulation factors**
RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(**protein S**; screening for blood coagulation defects using metal ions)

IT **Blood analysis**
Blood coagulation
Photometry
Test kits
(screening for blood coagulation defects using metal ions)

IT Enzymes, biological studies
RL: ARG (Analytical reagent use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(screening for blood coagulation defects using metal ions)

IT Collagens, biological studies
Kaolin, biological studies
Phosphatidylcholines, biological studies
Phosphatidylserines
Phospholipids, biological studies
Reagents
Sphingomyelins
Thrombomodulin
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(screening for blood coagulation defects using metal ions)

IT **Blood-coagulation factors**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(screening for blood coagulation defects using metal ions)

IT **Vipera russelli**
(**snake venom** enzyme of; screening for blood coagulation defects using metal ions)

IT **Agkistrodon**
Agkistrodon contortrix contortrix
(**snake venom** enzymes of; screening for blood coagulation defects using metal ions)

IT **Venoms**
(**snake**, enzymes of; screening for blood coagulation defects using metal ions)

IT **67869-62-9**
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(as fibrin polymn. inhibitor; screening for blood coagulation defects using metal ions)

IT 91-64-5D, Coumarin, derivs. 100-01-6D, p-Nitroaniline, derivs. 3682-14-2D, Isoluminol, derivs. 25168-10-9D, Naphthylamine, derivs.
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(as leaving group on enzyme substrate; screening for blood coagulation defects using metal ions)

IT 60457-00-3, S-2222 83160-48-9, CBS 31.39 88803-90-1, Spectrozyme Xa 133943-48-3, S-2765
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical

study); BIOL (Biological study); PROC (Process); USES (Uses)
(as photometric substrate for Factor Xa; screening for blood coagulation defects using metal ions)

IT 36335-67-8, S-2846 62354-65-8, S-2238 72194-57-1, S-2366 88793-93-5, Spectrozyme TH 106775-37-5, CBS 34.47 244085-35-6, S 2796
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(as photometric substrate for thrombin; screening for blood coagulation defects using metal ions)

IT **60202-16-6, Protein C**
RL: ANT (Analyte); ARG (Analytical reagent use); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(screening for blood coagulation defects using metal ions)

IT **9001-24-5D**, Blood-coagulation factor V, mutants
RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(screening for blood coagulation defects using metal ions)

IT **9002-04-4**, Thrombin **9002-05-5**, Blood factor Xa
RL: ARG (Analytical reagent use); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(screening for blood coagulation defects using metal ions)

IT **9001-24-5**, Blood-coagulation factor V **9001-25-6**, Blood-coagulation factor VII **9001-26-7**, Prothrombin **9001-28-9**, Factor IX **9001-29-0**, Factor X **42617-41-4**, Activated **Protein C** **65312-43-8**, Factor VIIa **65522-14-7**, Factor Va 72162-96-0, Thromboplastin **72175-66-7**, Blood-coagulation Factor VIIIa **113189-02-9**, Factor VIII
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(screening for blood coagulation defects using metal ions)

IT 476-66-4, Ellagic acid 7631-86-9, Silica, biological studies 7773-01-5, Manganese chloride 7785-87-7, Manganese sulfate 7786-30-3, **Magnesium** chloride, biological studies 10043-52-4, **Calcium** chloride, biological studies 10377-60-3, **Magnesium** nitrate **14127-61-8, Calcium ion**, biological studies 14701-22-5, Ni2+, biological studies 15158-11-9, Cu2+, biological studies 16397-91-4, Mn2+, biological studies 17493-86-6, Cuprous ion, biological studies **22537-22-0**, **Mg2+**, biological studies 22537-39-9, Sr2+, biological studies 23713-49-7, Zn2+, biological studies **37203-61-5**, Blood-coagulation Factor XIa **37203-62-6**, Blood-coagulation Factor XIIa **37316-87-3**, Blood-coagulation Factor IXa 69670-93-5, Cephotest 110617-83-9, Protac C
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(screening for blood coagulation defects using metal **ions**)

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Bartl Knut; US 5001069 A 1991 HCAPLUS
(2) Baxter Diagnostics Inc; EP 0567636 A 1993 HCAPLUS
(3) Baxter Diagnostics Inc; WO 9310262 A 1993 HCAPLUS
(4) Bernardo, M; JOURNAL OF BIOLOGICAL CHEMISTRY 1993, V268(17), P12468 HCAPLUS
(5) Butenas, S; BIOCHEMISTRY 1994, V33(11), P3449 HCAPLUS
(6) Heeb, M; JOURNAL OF BIOLOGICAL CHEMISTRY 1991, V266(26), P17606 HCAPLUS

(7) Liebman, H; JOURNAL OF BIOLOGICAL CHEMISTRY 1987, V262(16), P7605 HCAPLUS
(8) Pedersen, A; THROMBOSIS AND HAEMOSTASIS 1991, V65(5), P528 HCAPLUS
(9) Proksch, G; US 5055412 A 1991 HCAPLUS
(10) Sekiya, F; JOURNAL OF BIOLOGICAL CHEMISTRY 1995, V270(24), P14325 HCAPLUS
(11) Shore, J; BIOCHEMISTRY 1987, V26(8), P2250 HCAPLUS
(12) Speck, R; US 5637452 A 1997 HCAPLUS

L123 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN **1998:899** HCAPLUS
DN **128:125568**
TI Evaluation of prothrombin time with use of highly diluted tissue factor reagent
AU Komiyama, Yutaka; Munakata, Machiko; Masuda, Midori; Kagawa, Hideo; Nomura, Shosaku; Fukuhara, Shirou; Takahashi, Hakuo
CS Dep. of Clinical Sciences and Laboratory of Medicine, Kansai Medical University, Moriguchi, 570, Japan
SO Nippon Kessen Shiketsu Gakkaishi (1997), 8(5), 376-381
CODEN: NKSGEL; ISSN: 0915-7441
PB Nippon Kessen Shiketsu Gakkai
DT Journal
LA Japanese
CC **9-16** (Biochemical Methods)
Section cross-reference(s): 14
AB Prothrombin time (PT) is an established screening method for hemorrhagic disorders. Recent progress of the biochem. of tissue factor (TF)-dependent coagulation pathway revealed that TF/factor VIIa complex activated factor IX rather than factor X. However, PT does not reflect the activity of factors IX and VIII, because of excess amt. of TF reagent in the assay system. In this study, we evaluated PT using highly dild. TF reagent (Dil-PT) and its clin. application. Coexistence of **magnesium** with **calcium ion** resulted in the shortening of Dil-PT. Dil-PT prolonged in accordance with the decrease of TF reagent, and prolongation was obsd. in factor VIII- and factor IX-deficient plasmas similarly to the factor X-, factor V-, factor VII- and factor II-deficient plasmas. On the contrary, prolonged clotting time of factor XI-, factor XII-, high mol. wt. kininogen- and plasma prekallikrein-deficient plasmas were the same as that of normal pooled plasma in the Dil-PT system. In the clin. samples, significant shortenings of Dil-PT and PT were obsd. in the patients with rhabdomyolysis. On the other hand, Dil-PT showed significant shortening in gestational toxicosis, but PT did not. These results suggest that Dil-PT reflect the activity of factors IX and VIII besides factors VII, X, V and II, and Dil-PT is a useful screening method that does not require specific reagents and app. for the detection of hypercoagulable state.
ST prothrombin time dild tissue factor reagent
IT Preeclampsia
(evaluation of prothrombin time with use of highly dild. tissue factor reagent)
IT Kininogens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(evaluation of prothrombin time with use of highly dild. tissue factor reagent)
IT Muscle, disease
(rhabdomyolysis; evaluation of prothrombin time with use of highly dild. tissue factor reagent)
IT **7439-95-4**, **Magnesium**, biological studies
7440-70-2, **Calcium**, biological studies **9001-24-5**
, Blood coagulation factor V **9001-26-7**, Prothrombin
9001-27-8, Factor VIII- **9001-28-9**, Factor IX
9035-58-9, Blood-coagulation factor III 9055-02-1, Prekallikrein
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(evaluation of prothrombin time with use of highly dild. tissue factor reagent)

L123 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN **1997:812219** HCAPLUS
DN **128:45572**
TI Pretreatment of fibrin complex-containing sample by addition of multivalent ions and dissociation agents prior to immunoassay
IN Adema, Enno; Gebert, Ulrike; Herz, Reinhard
PA Boehringer Mannheim GmbH, Germany
SO Ger. Offen., 8 pp.
CODEN: GWXXBX
DT Patent
LA German
IC ICM G01N001-28
ICS G01N033-577; C12Q001-56
CC **9-4** (Biochemical Methods)
Section cross-reference(s): 15
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI DE 19621726	A1	19971204	DE 1996-19621726	19960530

AB Fibrin-contg. body fluid samples are treated with a fibrin-dissocn. reagent contg. a dissocn. agent and a polyvalent metal cation in a concn. not sufficient to cause dissocn. of the fibrin monomer complex; the treated sample is then incubated at acidic pH (.ltoreq.5, preferably .ltoreq.3) prior to immobilized-antibody immunoassay for fibrin. The dissocn. agent is chosen from chaotropic denaturants and H-bond-rupturing agents, such as thiocyanates, iodides, **Mg** compds., guanidinium compds., urea, salicylic acid, 4-toluenesulfonic acid, Ph acetate, 3,5-diiodo-2-hydroxybenzoic acid, trichloroacetic acid, or salts. The polyvalent metal **ions** are chosen from alk. earth metals and transition metals (esp. **Mg**, **Ca**, Sr, Ba, Mn2+, and Cd **ions**).
ST fibrin monomer dissocn treatment immunoassay; coagulation blood fibrin immunoassay; thiocyanate fibrin dissocn immunoassay; polyvalent metal fibrin dissocn immunoassay
IT Dissociation
(agents; pretreatment of fibrin complex-contg. sample by addn. of multivalent ions and dissocn. agents prior to immunoassay)
IT Denaturants
(chaotropic; pretreatment of fibrin complex-contg. sample by addn. of multivalent ions and dissocn. agents prior to immunoassay)
IT Body fluid
(fibrin-contg.; pretreatment of fibrin complex-contg. sample by addn. of multivalent ions and dissocn. agents prior to immunoassay)
IT Antibodies
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(immobilized, for immunoassay of fibrin; pretreatment of fibrin complex-contg. sample by addn. of multivalent ions and dissocn. agents prior to immunoassay)
IT Alkali metals, analysis
Alkaline earth metals
Halides
Transition metals, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(ions, dissocn. reagent contg.; pretreatment of fibrin complex-contg. sample by addn. of multivalent ions and dissocn. agents prior to immunoassay)
IT Immunoassay
(of fibrin; pretreatment of fibrin complex-contg. sample by addn. of multivalent ions and dissocn. agents prior to immunoassay)
IT **Blood coagulation**
Blood plasma
(pretreatment of fibrin complex-contg. sample by addn. of multivalent

ions and dissocn. agents prior to immunoassay)

IT Fibrins
RL: ANT (Analyte); ANST (Analytical study)
(pretreatment of fibrin complex-contg. sample by addn. of multivalent ions and dissocn. agents prior to immunoassay)

IT 57-13-6, Urea, analysis 69-72-7, Salicylic acid, analysis 76-03-9, Trichloroacetic acid, analysis 104-15-4, 4-Toluenesulfonic acid, analysis 122-79-2, Phenyl acetate 133-91-5, 3,5-Diiodo-2-hydroxybenzoic acid 302-04-5, Thiocyanate, analysis **7439-95-4D**, **Magnesium**, salts, analysis 7447-40-7, Potassium chloride, analysis 7647-14-5, Sodium chloride, analysis 7647-17-8, Cesium chloride, analysis 7791-11-9, Rubidium chloride, analysis **14127-61-8, Calcium ion**, analysis 14797-55-8, Nitrate ion, analysis 14866-68-3, Chlorate ion 16397-91-4, Manganese(II) ion, analysis 20461-54-5, Iodide, analysis **22537-22-0, Magnesium ion**, analysis 22537-39-9, Strontium ion, analysis 22537-48-0, Cadmium, ion (Cd2+), analysis 22541-12-4, Barium ion, analysis 25215-10-5D, Guanidinium, salts
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(dissocn. reagent contg.; pretreatment of fibrin complex-contg. sample by addn. of multivalent **ions** and dissocn. agents prior to immunoassay)

L123 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN **1997:72373** HCAPLUS
DN **126:86820**
TI Reagent for measuring blood coagulation activity
IN Morita, Takashi
PA Eisai Co., Ltd., Japan; Morita, Takashi
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12Q001-56
CC **9-15** (Biochemical Methods)
Section cross-reference(s): 7

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9638585	A1	19961205	WO 1996-JP1488	19960531
	W: NO, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	JP 08327631	A2	19961213	JP 1995-134998	19950601
PRAI	JP 1995-134998		19950601		

AB Provided are a reagent for measuring blood coagulation activity mediated by blood-coagulation factor IX, characterized in that the reagent contains **Mg2+** ions, and a method of measuring blood coagulation activity mediated by blood-coagulation factor IX, which comprises adding **Mg2+** ions to a reaction soln. for measuring the blood coagulation activity.

ST blood coagulation detn reagent **magnesium**; factor IX activation **magnesium** coagulation detn

IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(anticoagulant; **magnesium**-contg. reagent for detg. factor IX-mediated blood coagulation)

IT **Blood coagulation**
Conformation
Tertiary structure
(**magnesium**-contg. reagent for detg. factor IX-mediated blood

coagulation)
IT Antibodies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(monoclonal; **magnesium**-contg. reagent for detg. factor IX-mediated blood coagulation)
IT **7440-70-2, Calcium**, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**magnesium**-contg. reagent for detg. factor IX-mediated blood coagulation)
IT **9001-28-9**, Factor IX
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(**magnesium**-contg. reagent for detg. factor IX-mediated blood coagulation)
IT **7439-95-4, Magnesium**, biological studies 37203-61-5, Factor XIa
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**magnesium**-contg. reagent for detg. factor IX-mediated blood coagulation)

L123 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN **1995:761808** HCAPLUS
DN **123:164691**
TI Blood coagulation retardants and devices
IN Lyon, Martha E.; Henderson, Paul; Malik, Sohail; Kenny, Margaret A.; Lyon, Andrew W.
PA University of Washington, USA
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12Q001-56
ICS G01N033-86
CC **9-16** (Biochemical Methods)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9514788	A1	19950601	WO 1994-US13537	19941123
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN				
	RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9511862	A1	19950613	AU 1995-11862	19941123
PRAI	US 1993-157880		19931124		
	WO 1994-US13537		19941123		

AB The invention provides methods of using anticoagulants to retard the coagulation of blood, so that properties and functions of blood, plasma, and blood cells may be detd. anal. The methods do not interfere with electrochem. techniques use to detect **divalent cations** and permit accurate anal. of many analytes within a single blood sample, which currently require sep. anticoagulated blood samples. The serine protease inhibitors used may be combined with each other or blood cell activation, aggregation, and adhesion inhibitors in mixts. that provide anticoagulant activity. The methods permit, for the first time, the possibility of using a single blood sample to perform a full range of

blood, plasma, and blood cell analyses. The anticoagulation effect of D-phenylalanyl-prolyl-arginyl chloromethyl ketone is detd.

ST blood coagulation retardant gas analyzer

IT Blood analysis
Blood coagulation
Gas analysis
Hematocrit
Pancreas
pH
(blood coagulation retardants and devices)

IT Albumins, analysis
Fatty acids, analysis
Prealbumins
Proteins, analysis
RL: ANT (Analyte); ANST (Analytical study)
(blood coagulation retardants and devices)

IT Annexins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(blood coagulation retardants and devices)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(monoclonal, blood coagulation retardants and devices)

IT 50-99-7, Glucose, analysis 57-88-5, Cholesterol, analysis 60-27-5, Creatinine 64-17-5, Ethanol, analysis 124-38-9, Carbon dioxide, analysis 635-65-4, Bilirubin, analysis **7439-95-4**, **Magnesium**, analysis 7440-09-7, Potassium, analysis 7440-23-5, Sodium, analysis **7440-70-2**, **Calcium**, analysis 7727-37-9, Nitrogen, analysis 7782-44-7, Oxygen, analysis 9000-92-4, Amylase 14265-44-2, Phosphate, analysis
RL: ANT (Analyte); ANST (Analytical study)
(blood coagulation retardants and devices)

IT 69024-84-6 71142-71-7 105806-65-3 130982-43-3 133247-60-6, Triflavin 139691-92-2, Serine protease inhibitor 141396-28-3 141426-89-3 167026-36-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(blood coagulation retardants and devices)

IT 9005-49-6, Heparin, biological studies 16887-00-6, Chloride, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(blood coagulation retardants and devices)

L123 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN **1991:118093** HCAPLUS
DN **114:118093**
TI Blood-coagulation factor-sensitive reagent containing ellagic acid/salt, **divalent metal** ion, and/or cephalin for blood coagulation test
IN Proksch, Gary J.
PA USA
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12Q001-56
ICS G01N033-86
CC **9-2** (Biochemical Methods)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9011368	A1	19901004	WO 1990-US1520	19900319

W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, RO, SD, SU
RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, DK, ES, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG
US 5055412 A 19911008 US 1989-326381 19890321
AU 9053502 A1 19901022 AU 1990-53502 19900319
PRAI US 1989-326381 19890321
WO 1990-US1520 19900319

AB A stable blood-coagulation factor-sensitive reagent for use in detn. of activated partial thromboplastin time (APTT) can be speedily prepd. by: (1) prepg. an ellagic acid/salt soln. at a predetd. molar concn. (e.g. 0.1 mM); (2) adding a cephalin to the soln.; (3) adding certain **divalent metal** ions (e.g. Cu2+, Co2+, Fe2+, Zn2+, etc.) to molar ratios 3-30 relative to the ellagic acid/salt concn.; and (4) adjusting the pH of the resulting soln. with a buffer (e.g. N-(2-hydroxyethyl)piperazine-N'-2-ethanesulfonic acid hemisodium salt) to .apprx.7.5. A reagent capable of forming a procoagulant reagent upon exposure to a source of cephalin can also be prepd. according to the same procedure except that the cephalin is not added and the molar ratio of the **divalent metal** ion is .ltoreq.3 but .gtoreq.0.1. This reagent may be used e.g. to det. platelets. Detailed procedures for prepg. several reagents are given and the sequence of the prepn. steps is emphasized. The reagents were used to det. APTT by centrifuging platelets from plasma and applying std. test procedures; they were sensitive to all coagulation factors except factor VII, XII, and platelets. One reagent was also used in a modified procedure to det. clotting time of platelet-contg. plasma for detecting platelet deficiency.

ST blood coagulation factor sensitive reagent; thromboplastin partial time detn; platelet deficiency detection blood

IT Lupus erythematosus
(blood coagulation inhibitor in, reagent sensitive to, prepn. of, for activated partial thromboplastin time detn. in blood coagulation test)

IT Cephalins
RL: ANST (Analytical study)
(blood-coagulation factor-sensitive reagent contg., for activated partial thromboplastin time detn.)

IT Blood platelet
(deficiency of, prediction of, by clotting time test)

IT **Blood coagulation**
(detn. of, by measuring activated partial thromboplastin time with blood-coagulation factor-sensitive reagent)

IT **Blood-coagulation factors**
RL: SPN (Synthetic preparation); PREP (Preparation)
(reagent sensitive to, prepn. of, for activated partial thromboplastin time detn. in blood coagulation test)

IT **Cations**
(**divalent**, blood-coagulation factor-sensitive reagent contg., for activated partial thromboplastin time detn.)

IT 476-66-4, Ellagic acid 7439-89-6, Iron, biological studies 7439-92-1, Lead, biological studies **7439-95-4, Magnesium,** biological studies 7439-96-5, Manganese, biological studies 7440-24-6, Strontium, biological studies 7440-48-4, Cobalt, biological studies 7440-50-8, Copper, biological studies 7440-66-6, Zinc, biological studies **7440-70-2, Calcium,** biological studies 122328-15-8, Sodium ellagate
RL: ANST (Analytical study)
(blood-coagulation factor-sensitive reagent contg., for activated partial thromboplastin time detn.)

IT 75277-39-3
RL: ANST (Analytical study)
(pH adjustment with, in blood-coagulation factor-sensitive reagent prepn., for activated partial thromboplastin time detn. in blood coagulation test)

IT **9001-29-0**, Blood-coagulation factor X
RL: ANST (Analytical study)
(reagent sensitive to, prepn. of, for activated partial thromboplastin time detn. in blood coagulation test)

L123 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN 1985:467885 HCAPLUS
DN 103:67885
TI Purification and isolation of blood clotting proteins using conformation specific antibodies
IN Furie, Bruce E.; Furie, Barbara C.; Liebman, Howard A.; Lewis, Richard M.
PA New England Medical Center Hospitals, Inc., USA
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07G007-00
ICS C07G007-04; A61K039-395
CC **9-2 (Biochemical Methods)**
Section cross-reference(s): 7, 15
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 8501941	A1	19850509	WO 1984-US1746	19841029
	W: DK, FI, JP, NL				
	RW: AT, BE, CH, DE, FR, GB, LU, NL, SE				
	EP 162078	A1	19851127	EP 1984-904241	19841029
	EP 162078	B1	19940914		
	R: AT, BE, CH, DE, FR, GB, LI, LU, NL, SE				
	JP 61500226	T2	19860206	JP 1984-504143	19841029
	JP 05077679	B4	19931027		
PRAI	US 1983-546364		19831028		
	WO 1984-US1746		19841029		

AB A method is described for the purifn. of mammalian proteins whose configuration is changed when complexed with a ligand (blood-coagulation factors, prothrombin, **protein C**, protein S, serum albumin, enzymes) which retains the structural and functional integrity of the proteins. The method was immobilized antibodies (monoclonal or polyclonal) which either specifically react with protein-ligand complexes and fail to react with the protein in the absence of the ligand, or which specifically react with ligand-free protein and fail to react with protein complexed with the ligand. The method involves contacting the protein in the presence of the ligand (**divalent** or trivalent **metal cation**) with immobilized antibody to form an immune complex, and contacting the immune complex with a chelating agent (EDTA) having higher affinity for the ligand than the protein (when the antibody used is specific for the ligand-stabilized conformer of the protein) or with the ligand (when the antibody used is specific for the nonligand stabilized protein) to release the protein from the immobilized antibody. For example, the method was used for the purifn. of human factor IX by using a conformation-specific rabbit polyclonal or murine monoclonal antifactor IX antibody-Sepharose column.

ST mammal protein purifn antibody; blood coagulation factor purifn antibody; enzyme purifn conformation specific antibody; immune complex antibody protein purifn; immunoaffinity chromatog protein purifn

IT Antibodies
RL: ANST (Analytical study)
(conformation-specific, in protein specification)

IT Albumins, blood serum
Blood-coagulation factors
Enzymes
Proteins
RL: PUR (Purification or recovery); PREP (Preparation)

(purifn. of, with conformation-specific antibodies)
IT Proteins
RL: PUR (Purification or recovery); PREP (Preparation)
(S, purifn. of, with conformation-specific antibodies)
IT **Cations**
(**divalent**, protein complexes with, in carbon purifn. with conformation-specific antibodies)
IT Immunochemical analysis
(immunoaffinity chromatog., for proteins)
IT Antibodies
RL: ANST (Analytical study)
(monoclonal, conformation-specific, in protein specification)
IT **7439-95-4D**, protein complexes 7439-96-5D, protein complexes
7440-50-8D, protein complexes 7440-54-2D, protein complexes
7440-70-2D, protein complexes
RL: ANST (Analytical study)
(in proteins purifn. with conformation-specific antibodies)
IT 60-00-4, uses and miscellaneous
RL: USES (Uses)
(in proteins purifn. with specific antibodies)
IT 9012-36-6D, reaction products with conformation-specific antibodies
RL: ANST (Analytical study)
(protein purifn. by chromatog. on)
IT **9001-24-5P 9001-25-6P 9001-26-7P**
9001-27-8P 9001-28-9P 9001-29-0P
60202-16-6P
RL: PUR (Purification or recovery); PREP (Preparation)
(purifn. of, with conformation-specific antibodies)

L123 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN **1981:187155** HCAPLUS
DN **94:187155**
TI Interaction of **calcium** with bovine plasma **protein C**
AU Amphlett, Godfrey W.; Kisiel, Walter; Castellino, Francis J.
CS Dep. Chem., Univ. Notre Dame, Notre Dame, IN, 46556, USA
SO Biochemistry (1981), 20(8), 2156-61
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
CC 6-3 (General Biochemistry)
AB The binding of 45Ca2+ to bovine plasma **protein C** (PC) and to activated bovine plasma **protein C** (APC) was examd. by equil. ultrafiltration at pH 7.4 and 25.degree.. Under these conditions, PC possesses 16.0 equiv **Ca2+** binding sites, of av. KD 8.7 .times. 10-4M, and APC contains 9.0 equiv **Ca2+** binding sites, with an av. KD of 4.3 .times. 10-4M. Both Mn2+ and Sr2+ readily displaced **Ca2+** from a **Ca2+**-PC complex, whereas **Mg2+** was less effective in this regard. The .alpha.-thrombin-catalyzed activation of PC was inhibited by the presence of **Ca2+**. A kinetic anal. of this effect demonstrated that it was, in large part, due to an increase in the Km of the reaction. Addn. of other **divalent cations**, e.g., Mn2+, Sr2+, and **Mg2+**, in place of **Ca2+** also inhibited the .alpha.-thrombin-catalyzed activation of PC in a manner which paralleled their ability to displace **Ca2+** from a **Ca2+**-PC complex. On the other hand, the activation of PC by the coagulant protein from Russell's viper venom was augmented by the presence of **Ca2+**. Other **divalent metal** ions, such as Sr2+ and Mn2+, in the absence of **Ca2+**, also weakly stimulated this reaction. **Mg2+**, on the other hand, was without notable effect.
ST **calcium** binding **protein C**
IT **Proteins**

RL: BIOL (Biological study)
(C, **calcium** binding by, of blood plasma)
IT Proteins
RL: BIOL (Biological study)
(coagulant, **protein C** activation by, of Russell's viper venom, **calcium** effect on)
IT **9002-04-4**
RL: BIOL (Biological study)
(**protein C** activation by, **calcium** effect on)
IT **7439-95-4**, biological studies 7439-96-5, biological studies
7440-24-6, biological studies **7440-70-2**, biological studies
RL: BIOL (Biological study)
(**protein C** of blood plasma binding of)

L123 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN **1978:504750** HCAPLUS
DN **89:104750**
TI Kinetic studies on the activation of human Factor X. The role of metal ions on the reaction catalyzed by the venom coagulant protein of Vipera russelli
AU Morris, Sam; Robey, Frank A.; Kosow, David P.
CS Blood Res. Lab., Am. Natl. Red. Cross, Bethesda, MD, USA
SO Journal of Biological Chemistry (1978), 253(13), 4604-8
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
CC 13-5 (Mammalian Biochemistry)
AB The effect of **Ca2+**, **Mg2+**, and Mn2+ on the initial rate of activation of human blood-coagulation factor X (I) by the venom coagulant protein of V. russelli was investigated. Neither **Mg2+** nor Mn2+ alone support the reaction. **Ca2+** is an essential activator and exhibits cooperative kinetics. Both **Mg2+** and Mn2+ enhance the reaction cooperatively when **Ca2+** is present at suboptimal concns. Similarly, **Ca2+** quenches the intrinsic fluorescence of human I in a cooperative manner. While neither **Mg2+** nor Mn2+ by themselves affect the fluorescence of human I, they decrease the cooperativity of the **Ca2+** binding to the protein as judged by Hill plots of the **Ca2+**-induced fluorescence quenching. EPR measurements indicate that there are 3 high affinity Mn2+ binding sites on human I which can also bind **Ca2+**. Pos. cooperativity was not obsd. for Mn2+ binding. These data indicate that **Ca2+** can cause a conformational change of the I mol. which allows the activation reaction to proceed. It is proposed that Mn2+ does not support the activation of human I because it cannot induce a necessary conformational change in the absence of **Ca2+**.
ST blood coagulation factor X activation cation
IT Kinetics, enzymic
(of activation, of blood-coagulation factor X, cation effect on)
IT **Venoms**
(of Vipera russelli, blood-coagulation factor X activation by coagulant protein of, cation effect on)
IT **9001-29-0**
RL: BIOL (Biological study)
(activation of, cation effect on enzymic)
IT **7439-95-4**, biological studies 7439-96-5, biological studies
7440-70-2, biological studies
RL: BIOL (Biological study)
(blood-coagulation factor X enzymic activation response to)

L123 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN 1978:34231 HCAPLUS
DN 88:34231

TI Reagents for determination of C-reactive protein
IN Okada, Tomoo
PA Eiken Chemical Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC G01N031-22
CC 9-13 (Biochemical Methods)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 52123295	A2	19771017	JP 1976-39577	19760408
	JP 60047552	B4	19851022		

AB C-reactive protein in body fluids was detd. by observing the aggregation of C-reactive protein in a system consisting of a buffer contg. choline chloride (5-40%), lecithin, cholesterol, and lipid-sol. dyes (1st soln.) and a 2nd soln. contg. 0.02-0.2M **Ca2+** and **Mg2+**; optionally, 0.2-1.0% Na polyanethole sulfonate also was added to the 2nd soln. Thus, the 1st soln. was prepd. by mixing 1 part of an alc. soln. contg. lecithin 0.9, Spam 60 0.5, and Sudan Black 0.1% with 9 parts of a veronal buffer (pH 8.6) contg. 10% choline chloride; a normal saline soln. contg. 0.02 M CaCl2 and MgCl2 was prepd. as the 2nd soln. Serum samples (0.05 mL) were placed on glass slides and mixed with equal (0.05 mL) amts. of the 2nd soln.; 1 drop of the 1st soln. then was added to the mixt., and the aggregate formation was obsd. after heating the mixt. at 56.degree. for 30 min. The size of aggregates formed was significantly correlated with the height of ppts. (in capillaries) formed during detn. of C-reactive protein by an immunopptn. method.
ST serum C reactive protein detn
IT **Blood analysis**
(C-reactive protein detn. in)
IT **Proteins**
RL: ANT (Analyte); ANST (Analytical study)
(**C**-reactive, detn. of, in blood serum)
IT 52993-95-0
RL: ANST (Analytical study)
(C-reactive protein detn. by reagent contg.)
IT 56996-93-1
RL: ANST (Analytical study)
(C-reactive protein detn. in blood serum with)

L123 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN **1976:573841** HCAPLUS
DN **85:173841**
TI Thrombin time in heparinized plasma. Reply to comments
AU Ts'ao, Chung-Hsin
CS Sch. Med., Northwest. Univ., Chicago, Ill., USA
SO Am. J. Clin. Pathol. (1976), 66(3), 613-14
CODEN: AJCPAI
DT Journal
LA English
CC **9-13** (Biochemical Methods)
Section cross-reference(s): 13
AB A polemic in response to J. A. Penner (1976) is given. Emphasis is placed on the need to understand better the anticoagulation action of heparin and the mechanism by which the thrombin time of heparinized plasma is affected by **divalent cations**. It is also stressed that although the effects of **divalent cations** on thrombin time are unknown, their roles in the prothrombin time (PT) and activated partial thromboplastin (APTT) time are understood better, and a table is presented showing the effects of **Ca2+**, **Mg2+**, Mn2+, and Sr2+ on PT and APTT of citrated plasma. In the absence of **Ca2+**,

thrombin generation is impaired, and consequently, the prolongation of PT and APTT under these circumstances results from insufficient thrombin generation.
ST thrombin time plasma heparin polemic
IT **Blood coagulation**
(thrombin time detn. in, in heparinized plasma)
IT 9002-04-4
RL: ANST (Analytical study)
(time, detn. in heparinized plasma)

L123 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN 1976:118146 HCAPLUS
DN 84:118146
TI Effects of source and concentration of thrombin, and **divalent cations**, on thrombin time of heparinized plasma
AU Ts'ao, Chung-Hsin; Raymond, Jane; Kolb, Todd; Lo, Rose
CS Coagulation Lab., Northwest. Mem. Hosp., Chicago, Ill., USA
SO Am. J. Clin. Pathol. (1976), 65(2), 206-12
CODEN: AJCPAI
DT Journal
LA English
CC **9-13** (Biochemical Methods)
Section cross-reference(s): 13
AB The effects of the source and concn. of thrombin, and those of **divalent cations**, on the thrombin time (TT) of heparinized plasma were investigated. A correlation between TT and the heparin concn. was obtained only when the thrombin was of human origin and when it was reconstituted in **divalent cation** solns. Relatively small variations in thrombin concn. resulted in marked differences in TT of heparinized plasma. Bovine thrombin gave a very prolonged TT of heparinized plasma compared with human thrombin, though the 2 thrombins gave identical TT values for nonheparinized control plasma. **Divalent cation** soln., in which thrombin was reconstituted, had a profound influence on TT of heparin plasma. When thrombin was reconstituted in 0.1M MnCl2 soln., the TT of a plasma contg. 0.5 unit heparin/ml was the same as that of a plasma contg. no heparin. The reliability of the thrombin time test as a means of monitoring heparin anticoagulation must be established by individual labs. via extensive testing of clin. samples.
ST thrombin time plasma heparin cation
IT **Blood analysis**
(thrombin time detn. in, heparin and **divalent cations** in relation to)
IT **7439-95-4**, biological studies 7439-96-5, biological studies 7440-24-6, biological studies **7440-70-2**, biological studies
RL: BIOL (Biological study)
(thrombin time detn. in heparinized blood plasma in relation to)
IT 9005-49-6
RL: ANST (Analytical study)
(thrombin time of heparinized blood plasma in relation to)
IT **9002-04-4**
RL: ANST (Analytical study)
(time, of heparinized blood plasma, thrombin and **divalent cations** in relation to)

L123 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2002 ACS
AN **1972:44319** HCAPLUS
DN **76:44319**
TI Role of alkaline earth metal ions in the activation of thromboplastin system
AU Nath, B. B.
CS Dep. Chem., Visya-Bharati, Santiniketan, India
SO Indian J. Biochem. Biophys. (1971), 8(3), 191-3

CODEN: IJBCAS
DT Journal
LA English
CC 13 (Mammalian Biochemistry)
AB Even though less effective, Sr2+ can be substituted for **Ca2+** in activating the thromboplastin system during the conversion of prothrombin to thrombin. Sr2+ coagulated decalcified plasma whereas Ba2+ and **Mg2+** were ineffective. When used at higher concns., **Mg2+** and Ba2+ increased thrombin clotting time. Sr2+ activated the thromboplastin system from tissue exts., but **Mg2+** and Ba2+ failed to do so. **Mg2+** and Ba2+, however, activated the thromboplastin system from Russell's viper venom. The obsd. coagulant action of these ions, when used with the venom, seems to be due not to activation of the venom by these ions but to the effect of available **Ca2+** exchanged by these ions.
ST thromboplastin activation **calcium** strontium; thrombin clotting **magnesium** barium
IT Alkaline earth metals
RL: BIOL (Biological study)
(in autoprothrombin C activation)
IT **Venoms**
(of Vipera russellii, autoprothrombin C of, alkaline earth metals in activation of)
IT **Vipera russelli**
(venom of, autoprothrombin C of, alkaline earth metals in activation of)
IT **9002-05-5**
RL: PROC (Process)
(activation of, alkaline earth metals in)
IT **7439-95-4**, biological studies 7440-24-6, biological studies 7440-39-3, biological studies **7440-70-2**, biological studies
RL: BIOL (Biological study)
(in autoprothrombin C activation)

=> fil wpix
FILE 'WPIX' ENTERED AT 15:13:33 ON 11 DEC 2002
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FILE LAST UPDATED: 9 DEC 2002 <20021209/UP>
MOST RECENT DERWENT UPDATE: 200279 <200279/DW>
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http://www.derwent.com/userguides/dwpi_guide.html <<<

=> d all abeq tech abex tot

L186 ANSWER 1 OF 13 WPIX (C) 2002 THOMSON DERWENT

AN **2002-540310** [58] WPIX
DNN **N2002-427886** DNC **C2002-153264**
TI Determination of complexed ions, atoms or molecules in blood by measuring the concentrations present in dialysate, employs a technique to prevent complex formation in the dialysate.
DC B04 P34 S03 S05
IN KRAEMER, M; NIER, V
PA (FREP) FRESENIUS MEDICAL CARE DEUT GMBH
CYC 27
PI EP 1217379 A2 20020626 (200258)* DE 15p G01N033-84
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
DE 10114283 A1 20020711 (200258) A61M001-16
JP 2002248165 A 20020903 (200273) 9p A61M001-14
ADT EP 1217379 A2 EP 2001-129707 20011213; DE 10114283 A1 DE 2001-10114283 20010323; JP 2002248165 A JP 2001-389926 20011221
PRAI DE 2001-10114283 20010323; DE 2000-10064179 20001222
IC ICM A61M001-14; A61M001-16; G01N033-84
ICS G01N033-48
AB EP 1217379 A UPAB: 20020910
NOVELTY - During determination of concentration by addition or extraction of a substance (I), complex formation by the ion, atom or molecule is prevented.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for dialysis apparatus comprised of a blood dialyser and filter, with a citrate addition system upstream of the dialysis and/or hemofiltration. An ion-containing substitution solution can be administered downstream. Further apparatus, measures ion the concentration in the dialysate.

Preferred Features: It is especially for determinations of **calcium** or **magnesium** ions. The procedure determines the ion concentration in the blood of a patient employing citrate **anticoagulation** hemodialysis and/or hemofiltration.

Preferred Procedure: (I) is an acid, and is added to prevent complex formation (by variation of pH, preferably alteration to 2-3) by either interruption of the supply of complexing agent, or releasing the ion form the ion-citrate complex by forming a (I)-citrate complex. Following interruption of citrate addition, ion concentration in the dialysate is measured repeatedly, determining the result on reaching a steady state, by extrapolation or by integrating the area of ion concentration as a function of the response function defined in terms of time. To approximate the dialysate ion concentration to that of the blood, the dialysis flow is reduced. Determination of ion concentration in the blood is effected without dialysis flow reduction, by calculation. An ion-sensitive sensor is used to measure ion concentration in the dialysate, and an alarm is given should the ion concentration in the patient's blood lie outside an acceptable range. Ion concentration on the blood-side chamber of the dialyser is determined without interrupting citrate supply, citrate supply is varied as a function of the result.

USE - To determination complexed ions, atoms or molecules, especially in the blood of a patient under dialysis.

ADVANTAGE - Reliable determinations are made of the ion, atom or molecule concentrations to be measured. Various options for prevention of complex formation are provided. The measurements are made economically, and without putting the patient at risk, and the determinations are made, not in the patient's blood, but in the dialysate, and so repeated taking of blood samples is obviated.

DESCRIPTION OF DRAWING(S) - A schematic diagram illustrates the basic principles of haemodialysis with citrate **anticoagulation** .(Drawing includes non-English language text)

Dwg.1/5

FS CPI EPI GMPI
FA AB; GI; DCN
MC CPI: B04-B04D; **B05-A01B**; B10-C02; B11-C08; **B12-K04E**

EPI: S03-E14H1; S05-C01; S05-H01
TECH UPTX: 20020910
TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - The ions of interest are **calcium** and/or **magnesium** ions.

L186 ANSWER 2 OF 13 WPIX (C) 2002 THOMSON DERWENT
AN **2002-489927** [52] WPIX
DNN **N2002-387327** DNC **C2002-139068**
TI Novel reagent useful for assessment of hemostatic potential of blood or plasma sample, comprises a **coagulation** activator.
DC B04 D16 P31
IN BAGLIN, T; DOOBAY, H; FISCHER, T J; LUDDINGTON, R; TEJIDOR, L
PA (ALKU) AKZO NOBEL NV
CYC 97
PI WO 2002034109 A2 20020502 (200252)* EN 44p A61B000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2002015382 A 20020506 (200257) A61B000-00
ADT WO 2002034109 A2 WO 2001-US32563 20011018; AU 2002015382 A AU 2002-15382 20011018
FDT AU 2002015382 A Based on WO 200234109
PRAI US 2000-698589 20001027
IC ICM A61B000-00
AB WO 200234109 A UPAB: 20020815
NOVELTY - A reagent (I) comprising a **coagulation** activator at a concentration of 11 picomolar or less, for assessment of the hemostatic potential of a blood or plasma sample, is new.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit for assessing the hemostatic potential of a test sample comprising a **coagulation** activator at a concentration of 11 picomolar or less, or the activator and instructions for diluting the activator, vesicles, a metal **divalent** cation or a metal salt capable of dissociating into a metal **divalent** cation, instructions for adding the activator, metal cation or metal salt and vesicles to a test sample, and instructions for assessing the hemostatic potential of the test sample.
USE - The reagent and the kit are useful for indicating a sample to be **hypocoagulable**, normal or **hypercoagulable**, depending upon the condition of the patient from which the sample was taken, for indicating a patient to have thrombotic tendency, hemorraghic tendency, or stasis, and also for assessing hemostatic potential of a blood or plasma sample (claimed). (I) is useful in the drug discovery and drug development processes by modifying the components or concentrations of the reagent. (I) is useful to determine the amount of plasma to be modified in order to restore **coagulability** to normal.
ADVANTAGE - The reagent allows for globally assessing both the **hypercoagulable** potential and **hypocoagulable** potential of a patient in a single assay, which is accurate, sensitive and easy. The test is simple and can be automated on standard laboratory **coagulometers**. The test is based on the rate of fibrin polymerization which allows detection of perturbances in the propagation, amplification and polymerization pathways, whereas in the traditional prothrombin time test, these parts of the **coagulation** pathway are overshadowed by the excessive amounts of Factor IIa produced by the initiation phase.
Dwg.0/10
FS CPI GMPI
FA AB; DCN
MC CPI: B04-B04D4; B04-B04D5; **B04-H19**; B04-N02; **B05-A01B**; **B05-A03A**; B05-B01P; B05-C07; B11-C08E; **B12-K04A**;

D05-H09

TECH UPTX: 20020815

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Reagent: (I) further comprises vesicles or liposomes. The vesicles comprise platelets, cellular debris, phospholipid vesicles (prepared by dilution, sonication, dialysis or extrusion), or platelet microparticles. The **coagulation** activator comprises tissue factor which is a recombinant or purified, truncated tissue factor, or cells expressing tissue factor on their surface. The tissue factor comprises a metal cation, especially a **divalent** metal cation such as **magnesium**, **calcium** or manganese or metal salt (5-50, preferably 15-35 mM), preferably a halide of **magnesium**, **calcium** or manganese, which dissociates into a metal cation. The tissue factor is at a concentration of 11, 8 or 6 picomolars, preferably 3 picomolars or less. The vesicles comprise phospholipids (at a concentration of 10-300 micromolar, preferably 50-200 micromolar) which comprise one or more of phosphatidylcholine, phosphatidylethanolamine or phosphatidylserine at a ratio of 0-10, preferably 10 %, by mole phosphatidylserine, 5-30, preferably 20 %, by mole phosphatidylethanolamine and the remainder, preferably 70 %, by mole phosphatidylcholine. The **coagulation** activator comprises tissue factor-rich mammalian tissue extracts, tissue factor purified from mammalian tissue or thromboplastin. The **coagulation** activator is capable of detecting defects in the initiation phase. (I) further comprises an activator of an **anticoagulant** pathway, preferably an activator of **protein C** which is a purified human or non-human mammalian thrombomodulin, soluble or membrane associated thrombomodulin, native thrombomodulin or thrombomodulin reconstituted with phospholipids, partially or fully glycosylated thrombomodulin, and fully deglycosylated thrombomodulin. The **protein C** activator (thrombomodulin) is at a concentration of 30 nanomolar or less, preferably 5-20 nanomolar. The thrombomodulin comprises heparin or heparin-like molecules and is relipidated with phospholipids comprising 10 % phosphatidylethanolamine. (I) further comprises buffers and/or stabilizers, or phospholipids. Preferred Kit: The kit further comprises **calcium** cation or **calcium** salt that dissociates into a **calcium** cation, and an activator of an **anticoagulant** pathway and instruction for adding the activator to the test sample. The thrombomodulin is provided separately from the **coagulation** activator, and mixed with heparin, heparin sulfate or heparin-like molecules. The kit has a first container having the **coagulation** activator which is a tissue factor at a concentration of 11 picomolars or less mixed with vesicles which are phospholipids at a concentration of 10-300 picomolar, a second container having a metal salt at a concentration of 5-50 mM, and third container having the **coagulation** activator mixed with vesicles and an activator of an **anticoagulant** pathway which is thrombomodulin at a concentration of 300 nanomolar or less.

ABEX

EXAMPLE - An assay was conducted for detecting the coagulability, by adding 50 micro-l of plasma to 50 micro-l of the activator and 50 micro-l of the start reagent which consisted of 0.25 M calcium chloride. A normal sample, a hypocoagulable sample (factor VIII deficient plasma) and a hypercoagulable plasma (protein S deficient plasma) were evaluated at various dilutions of the activator. The activator was diluted with a buffer at two dilutions, 1:100 and 1:50000 of its original concentration. The assay was conducted at 37 degrees C, and the reaction was monitored at 580 nm for 300 seconds. Endpoints were calculated for time and rate indices of clot formation. The ratio of the endpoint of reagent dilution (x) for specimen/endpoint of reagent dilution (y) for specimen to the endpoint of reagent dilution (x) for npp/endpoint of reagent dilution (y) for npp was calculated, where x is 1:100 dilution and y is a series of dilutions. The results were expressed as the magnitude of deviation at a given dilution or as the dilution required to deviate from ideal (normal

value or normal range). As the dilution of the reagent was greater (y became larger) the results for the two abnormal plasmas (the hypercoagulable and hypocoagulable plasmas) tested began to deviate from the calculated endpoints or ratios of the normal plasma. The hypocoagulable specimen produced ratios that were greater than 1 and the hypercoagulable specimen had ratios that were less than 1 for the endpoint (clot time)/ratio combination.

L186 ANSWER 3 OF 13 WPIX (C) 2002 THOMSON DERWENT
AN **2002-463332** [49] WPIX
DNN **N2002-365287** DNC **C2002-131735**
TI Determining hyper- or **hypocoagulable** condition of a patient, comprises initiating **coagulation** in patient sample by fibrin polymerization activator and monitoring formation of fibrin polymer to drive time dependent profile.
DC B04 D16 P31
IN BAGLIN, T; FISCHER, T J; TEJIDOR, L
PA (ALKU) AKZO NOBEL NV
CYC 97
PI WO 2002034110 A2 20020502 (200249)* EN 68p A61B000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2002014619 A 20020506 (200257) C12Q001-56 <--
ADT WO 2002034110 A2 WO 2001-US32564 20011018; AU 2002014619 A AU 2002-14619 20011018
FDT AU 2002014619 A Based on WO 200234110
PRAI US 2000-697934 20001027
IC ICM A61B000-00; **C12Q001-56**
ICS C12Q001-00
AB WO 200234110 A UPAB: 20020802
NOVELTY - Determining (M1) if a patient is **hypercoagulable**, **hypocoagulable** or normal, comprises initiating **coagulation** in the test sample of patient in the presence of an activator for carrying out intrinsic tenase-dependent fibrin polymerization (IP), and monitoring formation of IP over time to drive a time-dependent profile, where the results determine whether the patient is hyper- or **hypocoagulable** , or normal, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) assessing the **coagulation** system in a test sample;

(2) detecting defects in the propagation and/or amplification phase in the **coagulation** system of a test sample;

(3) monitoring an antithrombotic or **procoagulant** pharmaceutical therapy;

(4) evaluating the efficacy of an antithrombotic or **procoagulant** pharmaceutical; and

(5) assessing the hemostatic potential of a sample.

ACTIVITY - Thrombolytic; **Anticoagulant; Coagulant** . No supporting data is given in the source material.

MECHANISM OF ACTION - None given in the source material.

USE - For determining if a patient is **hypercoagulable**, **hypocoagulable** or normal, for assessing the **coagulation** system in a test sample, monitoring an antithrombotic or **procoagulant** pharmaceutical therapy, evaluating the efficacy of an antithrombotic or **procoagulant** pharmaceutical and assessing hemostatic potential of a sample (claimed). The method is useful for assessing the hemostatic potential of a sample. The method is also useful for determining how much the plasma needs to be modified in order to restore **coagulability** to normal.

ADVANTAGE - The method allows for globally assessing both the **hypercoagulable** potential and **hypocoagulable** potential of a patient in a single assay. The method is accurate and easy to use. Disturbances in the propagation and amplification loops are accessible in this method, whereas in the traditional prothrombin (PT) test, the parts of the **coagulation** pathway are overshadowed by the excessive amounts of Factor IIa produced by the initiation phase.

Dwg.0/10

FS CPI GMPI

FA AB; DCN

MC CPI: B04-B04D; **B04-H19**; B11-C07B2; **B12-K04A2**; B14-F04; B14-F08; **D05-H09**

TECH UPTX: 20020802

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The time-dependent profile, at least part of which includes initiation of clot formation, overall change in profile, slope of profile after initiation of clot formation and/or acceleration at the time of clot initiation, is compared to a time-dependent profile of a known sample. At least two time-dependent fibrin polymerization profiles are obtained, an additional profile obtained for a known sample from computer memory or by adding the activator at least one concentration to a known sample and monitoring the formation of fibrin polymerization over time. At least two time-dependent fibrin polymerization profiles are obtained for two different activator concentrations, and/or one or more profiles for a known sample at one or more activator concentrations. Parameter from each time-dependent fibrin polymerization profile having varying activator concentrations is determined and a concentration at which at least one parameter of the sample being tested deviates from normal is determined. The parameter is the index and value of the minimum of first derivative, the time index and value for the minimum and maximum of the second derivative or overall magnitude of change. The part is rate of acceleration of fibrin polymerization compared to known sample. A difference or ratio of parameters for test sample and normal sample are determined. Parameter is clot time and a ratio of clot times at different activator concentrations is determined. The parameter includes the time of initiation of clot formation, rate of clot formation, maximum acceleration of clot formation, turbidity at a predetermined time period or total change in turbidity. The parameters are measures of defects in the thrombin propagation and/or amplification phases. A ratio of one parameter in test and normal sample, and ratio for multiple concentrations of activator, are determined. A concentration at which ratio departs from 1 is determined. An activator of one or more **anticoagulant** pathways, and an activator of **protein C** e.g. thrombomodulin or its derivatives given in the specification are added. A fibrin polymerization profile is obtained with and without thrombomodulin. The activator comprises tissue factor and phospholipids. A metal salt (e.g. halide of **magnesium**, **calcium** or manganese) which dissociates into a metal **divalent** cation when added to the test sample, is added as part of the activator. The activator comprises homogenized cerebral tissue. M1 further involves adding phopholipids together with or separately from the activator, adding buffers and/or stabilizers to the test sample e.g. patient plasma sample. The time dependent measurement profile is an optical absorbance or transmittance profile provided on an automated analyzer. A visible light beam is directed through a container holding the test sample and activator, and light absorbed or transmitted is monitored to form the time dependent measurement profile. The activator comprises recombinant or purified tissue factor, truncated tissue factor or cells expressing tissue factor on their surface, sufficiently diluted to determine **hypercoagulable**, normal or **hypocoagulable** depending upon the condition of the patient. Defects in formation of intrinsic tenase complex are detected. One or more endpoints from the time-dependent measurement profile are calculated, the endpoints selected from the time of clot initiation and the rate of polymerization. Sample is

whole blood or platelet rich plasma. M1 further involves adding vesicles (e.g. platelets, cellular debris, phospholipid vesicles or platelet microparticles) to the test sample. M1 further involves adding less than 11 pM concentration of tissue factor that generates intrinsic dependent fibrin polymerization in the patient sample, measuring formation of fibrin polymerization, and determining whether the patient is **hypercoagulable**, normal or **hypocoagulable**, based on the measured fibrin polymerization. Fibrin polymerization profile is obtained at multiple concentrations of activator which triggers thrombin explosion. The fibrin polymerization measurement is used to adjust the patient's therapy to result in a fibrin polymerization profile approximating normal.

ABEX

EXAMPLE - The assay was conducted by adding 50 micro liter of plasma to 50 micro liter of the activator and then adding 50 micro liter of the start reagent. A normal sample, a hypocoagulable sample (Factor VIII deficient plasma) and a hypercoagulable plasma (protein S deficient plasma) were evaluated at various dilutions of the activator. The activator was a commercially available thromboplastin diluted with a buffer at two dilutions, a 1:100 and 1:500000 of its original concentration. The start reagent consisted of 0.25 M Calcium chloride. The assay was conducted at 37 degrees C and the reaction was monitored at 580 nm for 300 seconds. Endpoints were calculated for time and rate indices of clot formation. Ratios of endpoints were compared to other dilutions and other samples. As the dilution of the reagent become greater, the results for the two abnormal plasmas (hypercoagulable and hypocoagulable plasmas) tested began to deviate from the calculated endpoints or ratios of the normal plasma. The results were expressed as the magnitude of deviation at a given dilution or as the dilution required to deviate from ideal (normal value or normal range). The hypercoagulable and hypocoagulable results deviating in opposite directions indicating the ability to differentiate between the two conditions, were shown graphically.

L186 ANSWER 4 OF 13 WPIX (C) 2002 THOMSON DERWENT
AN 2002-404826 [43] WPIX
DNN N2002-317801 DNC C2002-113706
TI New method of analyzing a sample e.g. blood sample involves modifying a polysaccharide in the sample to contain a signature component and detecting the presence of the signature component.
DC B04 S03
IN LIU, D; QI, Y; SASISEKHARAN, R; SHRIVER, Z; SUNDARAM, M; VENKATARAMAN, G; QI, Y W
PA (MASI) MASSACHUSETTS INST TECHNOLOGY
CYC 97
PI WO 2002023190 A2 20020321 (200243)* EN 105p G01N033-50 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001092618 A 20020326 (200251) G01N033-50 <--
A61K031-715
US 2002169143 A1 20021114 (200277)
ADT WO 2002023190 A2 WO 2001-US28457 20010912; AU 2001092618 A AU 2001-92618 20010912; US 2002169143 A1 Provisional US 2000-231994P 20000912, US 2001-951138 20010912
FDT AU 2001092618 A Based on WO 200223190
PRAI US 2000-231994P 20000912; US 2001-951138 20010912
IC ICM A61K031-715; **G01N033-50**
ICS **G01N033-00**
AB WO 200223190 A UPAB: 20020709
NOVELTY - Analysis of a sample involves applying an experimental constraint to a polysaccharide in the sample to produce a modified polysaccharide, having a signature component, detecting the presence of

the signature component, in the sample as an indication that the polysaccharide is present in the sample and determining the presence or absence of the signature component to analyze the sample.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a kit for analyzing a polysaccharide sample comprising a control composition for identifying a signature component of a polysaccharide and instructions for applying the experimental constraint to the polysaccharide sample;

(2) evaluating the quality of a polysaccharide sample involving identifying a component within the polysaccharide sample, determining the amount of component, which indicates the quality of the sample;

(3) a computer-implemented method for generating a data structure, tangibly embodied in a computer-readable medium, representing a quantitative value of a component of a polysaccharide involving performing the calculation by the equation % relative amount (PRA) = RF x AUC %R (where RF is response factor, AUC %R is % relative AUC(100 x AUCc)/AUCT)), AUCc is the area under the cure for one component, AUCT is the sum of the area under the curve for all components);

(4) production of a composition of glycosaminoglycans involving salt precipitating a glycosaminoglycans-containing sample in a solvent to produce a first higher molecular weight fraction and second molecular weight fraction of isolated low molecular weight heparin (LMWH), and processing the second fraction of isolated LMWH to produce a concentrated LMWH preparation;

(5) treating a subject involving administering a composition of LMWH having an identified level of AT-binding sequence; and

(6) a composition comprising a LMWH preparation containing disulfated disaccharide (at least 15%), trisulfated disaccharide (75%), monosulfated disaccharide (3-5%) and 4-7 tetrasaccharide (at least 2%).

ACTIVITY - Thrombolytic; **Anticoagulant**; Cytostatic.

MECHANISM OF ACTION - Cancer cell growth inhibitor.

USE - For monitoring the presence of active components; for determining the amount of active components in the sample (e.g. pharmaceutical product, biological sample, blood sample). The signature component is used to identify biologically active molecules, screen a library. The LMWH composition is used for treating venous or arterial thromboembolic disease (all claimed). The LMWH composition is used for preventing **coagulation**, angiogenesis, neovascularization and psoriasis; for treating and/or preventing tumor cell proliferation or metastasis e.g. biliary tract cancer, brain cancer, etc.; in, in vitro assays e.g. quality control sample; for treating local inflammation, cerebral ischemia and stroke

ADVANTAGE - The method prepares the composition having enhanced therapeutic activity and can remove the regions, which are responsible for the side effects.

Dwg.0/13

FS CPI EPI

FA AB; DCN

MC CPI: B04-C02E1; B07-A02B; B11-C08D1; B11-C08D2; **B12-K04A**; B14-C03; B14-F02D1; B14-F02F2; B14-F04; B14-H01; B14-N16; B14-N17C

EPI: S03-E14H

TECH UPTX: 20020709

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Components: The signature component is biologically active (preferably biologically active portion of a polysaccharide) or is biologically inactive. The biologically active portion of polysaccharide is a tetrasaccharide of either the AT-III or FGF binding domain of heparin. The polysaccharide is glycosaminoglycan, LMWH, heparin, biotechnologically prepared heparin, chemically modified heparin, synthetic heparin or heparan sulfate. The signature component is one of the peaks corresponding to any one of DELTAUH(NAC,6S)GH(NS,3S,6S), DELTAUH(NS,6S)GH(NS,3S,6S); DELTAUH(NAC,6S)GH(NS,3S); or DELTAUH(NS,6S)GH(NS,3S). The solvent is polar solvent selected from H2O,

ethanol and/or acetone (preferably the mixture). LMWH is isolated or synthetic. LMWH preparation have an anti-Xa activity of at least 150 IU/ **mg** and ratio of anti-factor Xa:anti-factor IIa activity of greater than 1 (preferably greater than 3, especially greater than 4, particularly greater than 5). The LMWH includes the peaks at, at least 3.5 (preferably 4, especially at least 5).
Preferred Process: The experimental constraint is capillary electrophoresis, high pressure liquid chromatography, gel permeation chromatography, nuclear magnetic resonance, digestion with an exoenzyme, digestion with an endoenzyme, chemical digestion, chemical modification or modification with an enzyme. A batch of polysaccharide and the signature component is used to monitor the purity of the batch by determining the amount of signature component in the batch. The presence of signature component in the sample is indicative of an active component in the sample or indicates the sample is lacking a specific activity. The amount of active components in the sample is determined by determining the amount of signature component in the sample. The method is performed on at least two sample and the relative amounts of signature component in each of the at least two samples is determined. The highest relative level of signature component is indicative of the most active sample. The polysaccharide in the sample is compared to a reference database of polysaccharides of identical size as the polysaccharide to provide a compositional analysis of the sample polysaccharide. The polysaccharides of the reference database have also been subjected to the same experimental constraints as the polysaccharide in the sample. The method of quality evaluation further involves calculating the PRA of each fraction present in the sample. The precipitation is carried out at 0 - 70 (preferably 4) degrees C. The second fraction is processed by an enzymatic digestion using Heparinase III enzyme or by chemical degradation. The chemical degradation involves oxidative depolymerization with H2O2 or CU+ and H2O2, deaminative cleavage with isoamyl nitrite, or nitrous acid, beta-eliminative cleavage with benzyl ester of heparin by alkaline treatment or by heparinase. The first fraction is purified to produce a purified LMWH preparation and then formulated in a pharmaceutical carrier. The concentrated LMWH preparation comprises intact AT-binding domain. Production of the composition further involves subjecting the second fraction to ion exchange chromatography prior to processing.

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Components: The salt used in the precipitation step is a salt of **divalent** cations and weak anions and is selected from barium, **calcium**, **magnesium**, strontium, copper, silver, gold, nickel, cadmium, zinc, mercury, beryllium, palladium, platinum, iron or tin. The **divalent** cations and weak anions are acetates of cations of elements of the periodic table having **divalent valency** (preferably barium acetate, **calcium** acetate, **magnesium** acetate, strontium acetate, copper acetate, nickel acetate or **calcium** chloride, especially barium acetate or **calcium** acetate).

ABEX

ADMINISTRATION - The composition is administered orally, subcutaneously, intravenously, by aerosol (claimed), intramuscularly, intraperitoneally, intranasally, intraatracheally, by inhalation, ocularly, vaginally and rectally in a dosage of 1 ng/kg - 100 mg/kg.

EXAMPLE - No relevant example given.

L186 ANSWER 5 OF 13 WPIX (C) 2002 THOMSON DERWENT
AN 2002-122222 [16] WPIX
DNN N2002-091675 DNC C2002-037464
TI Detection of a complex of lipoprotein and an acute phase protein useful for predicting an increased probability of system failure or mortality involves adding a reagent to a sample, and measuring the formed complex over time.

DC B04 S03
IN DOWNEY, C; FISCHER, T J; NESHEIM, M; SAMIS, J A; TEJIDOR, L; TOH, C H; WALKER, J B
PA (ALKU) AKZO NOBEL NV
CYC 96
PI WO 2001096864 A2 20011220 (200216)* EN 83p G01N033-49 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001066795 A 20011224 (200227) G01N033-49 <--
ADT WO 2001096864 A2 WO 2001-US18611 20010608; AU 2001066795 A AU 2001-66795 20010608
FDT AU 2001066795 A Based on WO 200196864
PRAI US 2000-591642 20000609
IC ICM **G01N033-49**

AB WO 200196864 A UPAB: 20020308
NOVELTY - Detection of a complex of lipoprotein and an acute phase **protein** involves: adding at least one reagent to a test sample from a patient in order to cause formation of the complex; measuring the formation of the complex over time so as to derive a time-dependent measurement profile; and determining a slop and/or a time-dependent measurement profile so as to diagnose a condition of the patient.

DETAILED DESCRIPTION - Detection of a complex of at least one human lipoprotein and at least one acute phase **protein** involves:

(a) adding at least one reagent to a test sample from a patient comprising at least one part of a blood sample from the patient in order to cause formation of the complex, while causing no fibrin polymerization;

(b) measuring the formation of the complex over time so as to derive a time-dependent measurement profile; and

(c) determining a slope and/or a time-dependent measurement profile so as to diagnose a condition of the patient.

INDEPENDENT CLAIMS are also included for the following:

(1) predicting an increased probability of system failure or mortality of a patient involving: obtaining a blood sample from a patient, obtaining plasma or serum from the blood sample, adding the reagent, taking at least one measurement of a parameter of the plasma or serum and correlating the measured parameter to complex formation if present, and correlating the complex formation to the probability of system failure or mortality of the patient; and

(2) testing the effectiveness of a therapeutic involving:

(a) taking a test sample from a test subject;

(b) adding a reagent which causes formation of the complex in the test sample;

(c) administering to the subject a therapeutic;

(d) repeating the steps (a) and (b); and

(e) determining if the amount of complex formed has changed.

USE - For predicting an increased probability of system failure or mortality in a patient; diagnosing and treating patient with hemostatic dysfunction (claimed).

ADVANTAGE - The method detects particular abnormality and also monitors the progression of the disease in a single patient. The method is not only useful as early diagnostic and single monitoring marker of disseminated intravascular **coagulation** (DIC), but the quantifiable and standardizable changes also allow for prognostatic applicability in clinical management.

DESCRIPTION OF DRAWING(S) - The figures illustrate transmittance waveform, on the activated partial thromboplastin time (APTT) assay. Figure A shows a normal appearance, and (B) shows a biphasic appearance. The clot time is indicated by an arrow.

Dwg.1/50

FS CPI EPI
FA AB; GI; DCN
MC CPI: B04-N05; B11-C07; **B12-K04A2**
EPI: S03-E14H; S03-E14H1
TECH UPTX: 20020308
TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Reagent: The reagent is metal ion (preferably **divalent** transition metal ion). The metal ion comprises at least one **calcium, magnesium,** manganese, iron or barium. Optionally a clot inhibitor is provided as part of the reagent or as part of an additional reagent added to the test sample. The reagent is capable of causing precipitate formation completely in the absence of fibrin polymerization. The precipitate inhibiting reagent comprises an apolipoprotein capable of binding to a lipoprotein-acute phase **protein** binding site. The precipitate inhibiting reagent is capable of inhibiting the association of **C** -reactive **protein** (CRP) with chylomicrons or their remnants, low density lipoprotein (LDL), very low density lipoprotein (VLDL) and/or intermediate density lipoprotein (IDL).

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Clot Inhibitor: The clot inhibitor comprises at least one of hirudin, heparin, PPACK (RTM), I2581 (RTM) or antithrombin.
Preferred Process: The formation of the complex is correlated to the increase probability of death of the patient, greater the formation of the complex, the greater the probability of death of the patient. The time-dependent measurement profile is an optical transmission profile, and greater the decrease of optical transmittance through the test sample, greater the formation of the complex. Diagnosing of the condition of the patient involves a prediction of the probability of mortality of the patient. The formation of the precipitate is measured at least once after time t0. A single endpoint measurement is made of precipitate formation after time t0. The amount of fibrin polymerization causes no change in optical transmittance. The method can also involve measuring a formation of a precipitate having the acute phase **protein** and the lipoprotein followed by addition of inhibiting reagent, before or after adding the precipitate causing reagent, which inhibits at least in part formation of the precipitate and determining the extent of inhibition of the inhibiting reagent. Several measurements are made after addition of the reagent in order to derive the time-dependent measurement profile. Rate of change of the measurements or a total change is determined and hemostatic dysfunction is determined based on the determined total and/or rate change. A single reagent is used prior to taking the measurements such as transmission or absorbance through the sample. The measurements are unaffected by clot formation due to lack of fibrin polymerization. The precipitate inhibiting reagent is either added after all or substantially all of the lipoprotein has become associated with acute phase **protein** so as to form the precipitate, or added prior to adding the precipitate causing reagent. Measurements are performed over time to derive time-dependent measurement profile. The formation of a complex and additional complex are measured over time to provide respective first and second time-dependent measurement profiles. The measured additional complex and measured initial complex together are correlated to a total amount of acute phase in the test phase. The formation of the complex can also be correlated to a concentration of the lipoprotein.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Components: The human lipoprotein comprises at least one chylomicrons or their remnants, VLDL, IDL, LDL or high density lipoprotein (HDL). The acute phase **protein** comprises **C**-reactive **protein** (CRP) and/or serum amyloid A (SAA) (preferably CRP).
Preferred Complex: A majority of the complex comprises CRP bound to VLDL.

ABEX
EXAMPLE - Freshly collected blood samples requiring a prothrombin (PT) or

activated partial thromboplastin time (APTT) were analyzed prospectively over a two week working period. The samples were taken in 0.105 M tri-sodium citrate in a ratio of 1 part anticoagulant to 9 parts whole blood. The platelet-poor plasma was analyzed on the multichannel discrete analyzer (MDA). The clot time were derived for PT (normal 11.2 - 15 seconds) using MDA simplastin LS (RTM) and APTT (normal 23-35 seconds) using MDA platelin LS (RTM) with 0.025 M calcium chloride. On analysis the transmittance waveform (TW) for APTT was performed at a wavelength of 580 nm. To ensure no cases of disseminated intravascular coagulation (DIC) were overlooked, a full DIC screen was performed to include the thrombin time; fibrinogen, and D-dimer levels on the Nyocard D-dimer (RTM). Platelet counts performed or an EDTA sample at the same time were recorded. A total of 1,470 samples from 747 patients were analyzed. 174 samples (11.9%) from 54 patients showed the bi-phasic waveform change. DIC was diagnosed in 41 patients with 30 of those requiring transfusion support with fresh frozen plasma, cryoprecipitate or platelets. 40 of the 41 patients with DIC showed the bi-phasic TW. The one false negative result (DIC without a bi-phasic TW) occurred in a patient with pre-eclampsia where the single sample showed a prolonged PT of 21 second, APTT of 44 seconds and raised D-dimer of 1.5 mg/liter. The results showed that the bi-phasic TW had a sensitivity of 97.6% and specificity of 98% for the diagnosis of DIC. The positive predictive value of the test was 74%, which increased with increasing steepness of the bi-phasic slope and decreasing levels of light transmittance.

L186 ANSWER 6 OF 13 WPIX (C) 2002 THOMSON DERWENT
AN 2001-420624 [45] WPIX
DNN N2001-311623 DNC C2001-127360
TI A method and a composition for the treatment of blood.
DC B04 P31 S03
PA (ASAH) ASAHI KASEI KOGYO KK
CYC 1
PI JP 2001083144 A 20010330 (200145)* 10p G01N033-48 <--
ADT JP 2001083144 A JP 1999-256245 19990909
PRAI JP 1999-256245 19990909
IC ICM **G01N033-48**
ICS A61B005-15
AB JP2001083144 A UPAB: 20010813
NOVELTY - A method for determination of reactions of blood cells.
DETAILED DESCRIPTION - A method for treatment of blood for cell reaction, particularly a mediator releasing reaction, particularly histamine, leukotriene, platelet activating factor (PAF) or cytokine by addition of a chelating agent, particularly ethylenediamine tetraacetic acid (EDTA), citric acid and/or oxalic acid, an **anticoagulant** without chelating activity, particularly heparin, plasmin, a protease, an azo dye, hirudin, dicumarol, thrombomodulin, an antibody to blood **coagulation** factor and/or a receptor which binds with the blood **coagulation** factor, and a metal salt, particularly chlorides, sulfates, carbonates, nitrates and/or phosphates, capable of dissolution of **bivalent** cation, particularly Ca, **Mg**, Mn, Zn, Cd and/or Cu, in an aqueous medium.
USE - Determination of reaction of blood cells in immune and allergic reaction.
ADVANTAGE - Determination of blood cell functions with satisfactory reproducibility without separation of blood cells.
Dwg.0/0
FS CPI EPI GMPI
FA AB; DCN
MC CPI: B04-B04D5; B04-C02; B04-G01; B04-H06; B04-L05C; **B05-A01B**; B05-C04; B05-C05; B05-C07; B06-A01; B10-C02; **B12-K04A**
EPI: S03-E14H
TECH UPTX: 20010813
TECHNOLOGY FOCUS - BIOLOGY - Treatment of blood cells.

ABEX
EXAMPLE - A blood sample of a healthy volunteer was treated with the claimed process and 7.8-8.0 % of coefficient of variation (CV) was obtained.

L186 ANSWER 7 OF 13 WPIX (C) 2002 THOMSON DERWENT
AN 2001-234924 [24] WPIX
CR 2000-514997 [46]
DNC C2001-070340
TI Detecting presence of hemostatic dysfunction, useful e.g. for diagnosing or monitoring of disseminated intravascular **coagulation**, by precipitation without fibrin polymerization.
DC B04
IN DOWNEY, C; FISCHER, T J; TOH, C H
PA (ALKU) AKZO NOBEL NV; (INMR) BIOMERIEUX SA
CYC 24
PI WO 2001013125 A1 20010222 (200124)* EN 91p G01N033-86 <--
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP KR US
AU 2000066179 A 20010313 (200134) G01N033-86 <--
EP 1200837 A1 20020502 (200236) EN G01N033-86 <--
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6429017 B1 20020806 (200254) G01N033-86 <--
KR 2002021811 A 20020322 (200264) G01N033-86 <--
ADT WO 2001013125 A1 WO 2000-US21022 20000802; AU 2000066179 A AU 2000-66179 20000802; EP 1200837 A1 EP 2000-953788 20000802, WO 2000-US21022 20000802; US 6429017 B1 CIP of US 1999-244340 19990204, US 1999-372954 19990812; KR 2002021811 A KR 2002-701897 20020209
FDT AU 2000066179 A Based on WO 200113125; EP 1200837 A1 Based on WO 200113125
PRAI US 1999-372954 19990812; US 1999-244340 19990204
IC ICM **G01N033-86**
AB WO 200113125 A UPAB: 20021031
NOVELTY - Method comprising treating a test sample, containing at least one component of blood, with a reagent (R) then measuring formation of a precipitate (P) over time to produce a time-dependent measurement profile. (R) forms a precipitate without significant polymerization of fibrin.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) determining presence of a complex (C) of **proteins**, comprising at least one of serum amyloid A and C -reactive **protein** (CRP);
(2) methods for determining possibility or probability of hemostatic dysfunction;
(3) method for monitoring an inflammatory condition using (R);
(4) method for diagnosing or treating hemostatic dysfunction (HD) using (R);
(5) immunoassay for diagnosing HD by detecting or quantifying CRP or a 300 kD **protein** (I); and
(6) method for testing new drugs on humans or animals having an inflammatory condition and/or HD.
ACTIVITY - **Anticoagulant**; Antithrombotic; Antiarthritic; Antiinflammatory; Antibacterial; Immunosuppressive; Antirheumatic.
MECHANISM OF ACTION - None given.
USE - (R) is used
(i) to diagnose hemostatic dysfunction (HD), particularly disseminated intravascular **coagulation** (DIC) or a condition that can lead to DIC, bleeding or thrombosis, also to optimize and monitor treatment,
(ii) to monitor an inflammatory condition (rheumatoid arthritis, sepsis or conditions caused by surgical trauma) or
(iii) to screen for new drugs for treatment of HD or inflammation.
ADVANTAGE - The method provides early indication of disseminated intravascular **coagulation**, and since it can be standardized and

made quantitative, it is suitable for prognosis and monitoring. It is simple and provides results quickly.

Dwg.0/29

FS CPI

FA AB; DCN

MC CPI: B04-B04D4; B04-B04D5; B04-N02; **B05-A01B**; **B05-A03A** ; B11-C07A; **B12-K04A2**; B14-A01; B14-C03; B14-C09B; B14-F04; B14-G02; B14-S12

TECH UPTX: 20010502

TECHNOLOGY FOCUS - BIOLOGY - Preferred reagent: (R) contains a metal ion, preferably **divalent**, and especially **calcium**, **magnesium**, manganese, iron or barium. It may also include a clotting inhibitor (CI), e.g. hirudin, heparin, PPACK, I2581 or antithrombin, or CI is provided in another reagent. (R) causes formation of (P) completely in absence of fibrin polymerization. Preferred precipitate: (P) comprises a **protein** of about 20 kD that is insoluble in saline, ethylenediamine tetraacetic acid or imidazole but soluble in 5 M urea. Preferred process: The formation of (P) is correlated with HD, with increased amounts of (P) indicating more severe dysfunction, and this can be quantified by constructing a reference curve for comparison with the patient sample. Especially the profile is an optical transmission or absorbance profile, with a greater reduction in transmission indicating a greater formation of (P). If any fibrin polymerization does occur, then it does not cause a change in optical transmittance. (R) is added in absence of clot-inducing reagents and either a single (end-point) measurement is made or several measurements, in which case HD is detected from the rate of change. The test sample is particularly plasma and the test may be repeated at different (R)/plasma ratios or at different times (to monitor progression or regression of disease). In method (a), a test sample (preferably blood or a blood component) is treated with an alcohol (especially (m)ethanol), CI and metal cation. The precipitate forms contains (**C**). In method (b), a **coagulation** reagent (specifically a prothrombin (PT) or activated partial thromboplastin time (APTT) reagent) is added to a sample and formation of fibrin monitored over time by measuring some parameter that changes due to addition of reagent. The rate of change of this parameter, before fibrin is formed in the sample, is determined and if the rate exceeds a predetermined value, a second aliquot of sample is treated with (R) and the formation of precipitate monitored over time. In method (**c**), some parameter indicative of (P) is measured over time, the rate of change calculated and the process repeated at various times, with a change in the rate indicating progression or regression of the inflammatory state. The parameter is optical transmission or absorbance. In method (d), a sample is treated with (R) and some parameter that changes due to formation of (P) is measured over time and its rate of change calculated. HD is diagnosed if the rate exceeds a predetermined level and appropriate treatment is administered, e.g. (i) antibiotic and/or CI or (ii) identification and correction of the underlying cause, e.g. administration of broad-spectrum antibiotic; evacuation of the uterus in abruptio placentae; blood replacement; administration of platelet concentrate (to correct thrombocytopenia), fresh plasma, blood factors and/or interleukin-1. The procedure may be repeated to optimize treatment. In method (e), a test sample is treated with a ligand (L) that can bind to CRP or (I), and this detected as part of a complex of **proteins** formed by adding a **divalent** metal cation. CRP may be intact, modified, cleaved or mutant. In method (f), a test sample is treated with (R) and kinetic or end-point measurements of precipitate formation made. A drug is then administered and the assay repeated, with an increase/decrease in precipitation indicating an effective drug.

ABEX

EXAMPLE - The plot of transmission against time in a standard activated partial thromboplastin time (APTT) assay is normally sigmoid but in patients with disseminated intravascular coagulation (DIC) it is biphasic,

with an initial region of low gradient and a subsequent region of steeper slope. The slope measured before start of clot formation is a significantly more specific and sensitive indicator of DIC than analysis of transmittance at a particular time. Particularly this slope was -0.001, or more negative, for all DIC patients and was -0.005 or more negative for 85 of 91 of them. Normal subjects, and those with abnormalities other than DIC, never had values more negative than -0.0002.

L186 ANSWER 8 OF 13 WPIX (C) 2002 THOMSON DERWENT
AN 1999-571846 [48] WPIX
DNN N1999-421410 DNC C1999-166879
TI New assays for determination of activity of components in the **Protein C anticoagulant** pathway, used for the study of diseases such as deep venous thrombosis and pulmonary embolism.
DC B04 D16 S03
IN **HALL, C M Y; ROSEN, B S**
PA (CHRO-N) CHROMOGENIX AB; (INLI) INSTRUMENTATION LAB SPA; (HALL-I) HALL C M Y; (ROSE-I) ROSEN B S
CYC 85
PI WO 9947699 A1 19990923 (199948)* EN 66p C12Q001-56 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
EP 947585 A1 19991006 (199948) EN C12Q001-56 <--
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
AU 9930339 A 19991011 (200008) C12Q001-56 <--
EP 947585 B1 20010725 (200143) EN C12Q001-56 <--
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
DE 69801210 E 20010830 (200158) C12Q001-56 <--
ES 2162361 T3 20011216 (200206) C12Q001-56 <--
US 6395501 B1 20020528 (200243) C12Q001-56 <--
US 2002115127 A1 20020822 (200258) C12Q001-56 <--
ADT WO 9947699 A1 WO 1999-EP1599 19990311; EP 947585 A1 EP 1998-105043 19980319; AU 9930339 A AU 1999-30339 19990311; EP 947585 B1 EP 1998-105043 19980319; DE 69801210 E DE 1998-601210 19980319, EP 1998-105043 19980319; ES 2162361 T3 EP 1998-105043 19980319; US 6395501 B1 US 1999-273413 19990319; US 2002115127 A1 Cont of US 1999-273413 19990319, US 2002-50441 20020116
FDT AU 9930339 A Based on WO 9947699; DE 69801210 E Based on EP 947585; ES 2162361 T3 Based on EP 947585
PRAI EP 1998-105043 19980319
IC ICM **C12Q001-56**
ICS **G01N033-86**
AB WO 9947699 A UPAB: 19991122
NOVELTY - New assays for the determination of activity of components in the **Protein C anticoagulant** pathway uses additional metal ions to improve the sensitivity of the assays.
DETAILED DESCRIPTION - (A) A novel in vitro photometric method for qualitative screening and quantitative determination of the functional activity of components of the **Protein C anticoagulant** pathway of blood **coagulation**, comprises measuring the conversion rate of an exogenous substrate by an enzyme. The activity of the enzyme is related to the **Protein C anticoagulant** activity, in a blood sample of a human comprising **coagulation** factors and the exogenous substrate after at least partial activation of **coagulation** through the intrinsic, extrinsic, or common pathway and triggering **coagulation** by:
(1) adding **calcium** ions, and
(2) comparing the conversion rate with the conversion rate of a

normal human blood sample determined in the same way, characterized by adding further metal(s) ions selected from **divalent** metal ions and **monovalent** copper ions to the sample.

INDEPENDENT CLAIMS are also included for the following:

(1) a kit for use in methods as in (A) comprising:

(a) an activator for the **Protein C**; or exogenous activated **Protein C** or exogenous **Protein C** together with an activator of **Protein C**;

(b) suitable **coagulation** activator;

(c) an exogenous synthetic substrate for either Factor Xa or thrombin comprising a photometrically measurable leaving group;

(d) **calcium** ions; and

(e) further metal(s) ions; and optionally

(f) **coagulation** factors; in separate containers and/or in containers comprising mixtures of at least two of the components in aqueous solution or in lyophilized form, and

(2) a reagent for use in methods as in (A) characterized by comprising the further metal(s) ions and at least one of the components as in (1a)-(1d) or (1f) in one container in aqueous solution or in lyophilized form.

USE - The methods can be used for the global screening for defects in the **Protein C anticoagulant** pathway of blood **coagulation**, for determination of free **Protein** S activity in a blood sample, for determination of **Protein** C activity in a blood sample, and for screening for Factor V mutations in a blood sample (claimed). They allow improved screening and diagnosing of defects in the **Protein C anticoagulant** pathway in investigation of patients with thromboembolic diseases such as deep venous thrombosis and/or pulmonary embolism.

ADVANTAGE - The addition of further metal ions in the presence of **calcium** ions enhances the **anticoagulant** activity of the **Protein C anticoagulant** pathway and provides for a high resolution between different levels of **Protein C** activity and **Protein** S activity, respectively, and a high discrimination for the presence of the FV:Q506 mutation, resulting in an improved sensitivity and specificity for detection of defects in components of the **Protein C anticoagulant** pathway with photometric and/or clotting methods.

Dwg.0/8

FS CPI EPI

FA AB; DCN

MC CPI: B04-B04D5; B04-C01A; B04-C01B; **B04-H19**; B04-L01; B04-N04; **B05-A01B**; **B05-A03**; B11-C07B2; B11-C08E3; B11-C09; **B12-K04A**; **B12-K04A2**; B14-F04; B14-F08; **D05-H09**

EPI: S03-E14H

TECH UPTX: 19991122

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Ion: The metal ions may be e.g. **Mg2+**, Mn2+, Zn2+, Cu2+, Ni2+, Sr2+ and/or Cu+.

TECHNOLOGY FOCUS - BIOLOGY - Preferred **Protein**: The **protein C** may be activated using a snake venom enzyme e.g. Protac (RTM) or thrombin optionally with thrombomodulin. **Coagulation** may also be activated using e.g. ellagic acid, collagen or silica. The medium may also contain a fibrin polymerization inhibitor e.g. Gly-Pro-Arg-Pro. The methods may also comprise use of a photometric substrate comprising a p-nitroaniline group (pNA) as a chromophoric leaving group, a naphthylamine or coumarine derivative group as a fluorophoric leaving group, or an isoluminolamide group as a luminophoric leaving group. The substrate for Factor Xa may be e.g. benzoyl-Ile-Glu-Gly-Arg-pNA , N-a-Z-D-Arg-Gly-Arg-pNA, CH3SO2-D-Leu-Gly-Arg-pNA, or MeO-CO-D-CHG-Gly-Arg-pNA. The substrate for

thrombin may be e.g. H-D-Phe-Pip-Arg-pNA, pyroGlu-Pro-Arg-pNA, H-D-Ala-Pro-Arg-pNA, Z-D-Arg-Sarc-Arg-pNA, AcOH-H-D-CHG-But-Arg-pNA, or H-D-HHT-Ala-Arg-pNA.

ABEX

EXAMPLE - The effect of manganese and magnesium ions on the determination of Protein C activity in a 3-stage chromogenic thrombin generation assay using the Protein C activation Protac C (RTM) was carried out using the following components: Samples: Protein C deficient plasma with an without addition of purified human Proteinc C to yield 0,. 0.1, 0.5 and 1.0 IU/ml of Protein C; Sample dilution: 1:41 in 25 mmol/L Tris-HCl pH 7.6, 20 mmol/L NaCl, 0.2% BSA; Protein C activator: Protac C (RTM) was used as a stock solution containing 10 U/ml. Final concentration during activation of Protein C = 0.17 U/ml. Mg2+ and Mn2+ ions were added to yield final concentrations during activation of Protein C of 0.4 and 0.04 mmol/L respectively. Reagent 1: Bovine Factor IXa, 180 pmol/L; Reagent 2: Phospholipids (a mixture of purified phospholipids containing 43% phosphatidylcholine, 27% phosphatidylserine and 30% sphingomycin), 60 mumol/L Gly-Pro-Arg-Pro, 0.36 mg/ml (polymerization inhibitor) Human Factor V, 0.2 U/ml; Chromogenic thrombin substrate: S-2796, 2 mmol/L. The assay was carried out as a 3-stage method comprising, in the first stage, combining 50 mul of diluted plasma with 50 mul of Protein C activator Protac C (RTM) and incubating this mixture for 3 minutes at 37degreesC, whereafter coagulation was achieved by adding 50 mul of Reagent 1 and 50 mul of Reagent 2 and incubating the mixture for 5 minutes at 37degreesC, whereafter, in the third stage, the substrate hydrolysis was carried out by adding 50 mul of the chromogenic thrombin substrate S-2796 and incubating for 4 minutes at 37degreesC. The reaction was then terminated by lowering the pH through addition of 50 mul of 20% acetic acid. The optical density (OD) of the samples in the microwells was then recorded at 405 and 490 nm and the difference in OD between 405 and 490 nm was calculated. The results showed that by including manganese and magnesium ions in a reaction system containing calcium ions, a strong enhancement of the anticoagulant activity was obtained, manifested by the fact that increasing concentrations of Protein C in the samples resulted in a much decreased absorbance, i.e. a much decreased thrombin generation. In contrast, in the presence of calcium ions alone, there was a much lower resolution in absorbance, i.e. in thrombin generation, at increasing Protein C concentrations. Thus, the addition of further metal ions constitutes an improved method for determination of Protein C activity.

L186 ANSWER 9 OF 13 WPIX (C) 2002 THOMSON DERWENT
AN **1998-495984** [42] WPIX
DNN **N1998-387347** DNC **C1998-149503**
TI Measurement of concentration of blood substitute in serum or plasma - comprises use of spectrophotometer to measure how sample absorbs or reflects radiation and incorporating this measurement in calibration algorithm.
DC B04 J04 S03
IN SAMSOONDAR, J
PA (CMET-N) CME TELEMETRIX INC
CYC 22
PI WO 9839634 A1 19980911 (199842)* EN 41p G01N021-27
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA JP KR US
EP 1023583 A1 20000802 (200038) EN G01N021-27
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2001513892 W 20010904 (200165) 35p G01N021-27
ADT WO 9839634 A1 WO 1997-CA759 19971016; EP 1023583 A1 EP 1997-944658 19971016, WO 1997-CA759 19971016; JP 2001513892 W WO 1997-CA759 19971016, JP 1998-538007 19971016
FDT EP 1023583 A1 Based on WO 9839634; JP 2001513892 W Based on WO 9839634
PRAI US 1997-38554P 19970303
IC ICM G01N021-27

ICS G01N033-49
AB WO 9839634 A UPAB: 19981021
To detect the concentration of a blood substitute interferent in a specimen, a spectrophotometer measures how the sample absorbs or reflects radiation. The concentration is determined by incorporating the measured absorbance in a calibration algorithm that has been generated for the interferent. Alternatively: (1) the specimen includes haemoglobin liberated from blood cells, turbidity and bile pigments, (2) the specimen is in a measured analyte concentration from a specimen. When modified the same method measures haemoglobin liberated from blood cells in the presence of a blood substitute interferent. Also claimed is a method for distinguishing true haemolysis from pseudo haemolysis caused by a blood substitute interferent uses the method as above. The algorithm for finding the interferent concentration includes the first derivative of absorbance at wavelengths of 541, 558, 600 and 616 nm. The algorithm for measuring haemoglobin includes the first derivative of absorbance at wavelengths of 558, 570 and 730 nm.
USE - The methods may be used for measuring the concentration of a blood substitute in a serum or plasma.
ADVANTAGE - Blood test results that have been effected by blood substitutes can be rapidly performed. The analyte may be potassium, sodium, chlorine, bicarbonate, **calcium**, **magnesium**, creatinine, urea, total protein, gamma glutamyl transfurase, aspartate amino transfurase, lactate dehydrogenase, creatine kinase, alkaline phosphatase or total bilirubin.
Dwg.0/7
FS CPI EPI
FA AB
MC CPI: B04-B04D2; **B04-B04D3**; B04-B04D5; **B12-K04**; J04-B01
EPI: S03-E04A1

L186 ANSWER 10 OF 13 WPIX (C) 2002 THOMSON DERWENT
AN **1997-034391** [03] WPIX
DNC **C1997-010817**
TI Factor IX mediated blood **coagulation** activity determn. - using reagent contg. added **magnesium** ions to stabilise Factor IX structure and give more accurate results.
DC B04 D16
IN MORITA, T
PA (EISA) EISAI CO LTD
CYC 20
PI WO 9638585 A1 19961205 (199703)* EN 35p C12Q001-56 <--
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: NO US
JP 08327631 A 19961213 (199709) 7p G01N033-86 <--
ADT WO 9638585 A1 WO 1996-JP1488 19960531; JP 08327631 A JP 1995-134998 19950601
PRAI JP 1995-134998 19950601
REP 3.Jnl.Ref; WO 9102813
IC ICM **C12Q001-56**; **G01N033-86**
ICA A61K049-00
AB WO 9638585 A UPAB: 19970115
A reagent for measuring blood **coagulation** activity mediated by blood **coagulation** factor IX (F9) contains **magnesium** (**Mg2+**) ions. Also claimed is a method for measuring blood **coagulation** activity mediated by F9 comprising adding **Mg2+** ions to a reaction soln. for measuring the blood **coagulation** activity.
USE - The **Mg2+** ions are typically added to solns. of clinical test reagents for measuring the prothrombin time, the partial prothromboplastin time or the activated partial thromboplastin time.
ADVANTAGE - The **Mg2+** ions stabilise the structure of F9 so that the measurements can be carried out more accurately under conditions

closer to physiological conditions. Both **Mg2+** ions and **calcium** ions (**Ca2+**) bind to blood **coagulation** factors having a gamma-carboxyglutamic acid (Gla) domain (to change the conformation to become recognisable by an activated protease), but **Mg2+** ions are specifically effective on F9 whereas **Ca2+** ions (previously used in such reagents) are effective on both F9 and factor X.
Dwg.2/5

FS CPI
FA AB; GI; DCN
MC CPI: B04-B04D5; **B05-A01B**; B11-C08E; **B12-K04A2**; **D05-H09**

L186 ANSWER 11 OF 13 WPIX (C) 2002 THOMSON DERWENT
AN **1996-130880** [14] WPIX
DNN **N1996-109976** DNC **C1996-040926**
TI Determn. of fibrinogen concn. in undiluted plasma sample - comprises addn. of novel reagent contg. thrombin or protease, in presence of high concn. of salt.
DC B04 D16 S03
IN ENOMOTO, M
PA (NNTR) NIPPON SHOJI KAISHA LTD; (AZWE-N) AZWELL INC; (NNTR) NIPPON SHOJI KK
CYC 5

PI	EP 699909	A2 19960306 (199614)*	EN	19p	G01N033-86	<--
	R: DE FR GB					
	JP 08070895	A 19960319 (199621)		10p	C12Q001-56	<--
	EP 699909	A3 19960619 (199635)			G01N033-86	<--
	US 5851836	A 19981222 (199907)			G01N033-49	
	JP 2994557	B2 19991227 (200006)		10p	C12Q001-56	<--
	EP 699909	B1 20011128 (200201)	EN		G01N033-86	<--
	R: DE FR GB					
	DE 69524161	E 20020110 (200211)			G01N033-86	<--

ADT EP 699909 A2 EP 1995-113736 19950901; JP 08070895 A JP 1994-209940 19940902; EP 699909 A3 EP 1995-113736 19950901; US 5851836 A US 1995-521868 19950831; JP 2994557 B2 JP 1994-209940 19940902; EP 699909 B1 EP 1995-113736 19950901; DE 69524161 E DE 1995-624161 19950901, EP 1995-113736 19950901
FDT JP 2994557 B2 Previous Publ. JP 08070895; DE 69524161 E Based on EP 699909
PRAI JP 1994-209940 19940902
REP 1.Jnl.Ref; EP 537490; EP 570354; EP 632270; JP 05219993; US 5292664; WO 9407145
IC ICM **C12Q001-56**; G01N033-49; **G01N033-86**
ICS C12Q001-37
AB EP 699909 A UPAB: 19960405
Method for determn. of fibrinogen (I) concn. comprises: (1) addn. of thrombin, or a protease having similar activity, to an undiluted sample (if plasma) in a reaction mixt. contg. a salt (II) at high concn., then (2) measurement of the **coagulation** time. The concn. of (II) is set at a level giving a **coagulation** time of 5-100 secs. at 37deg.C. using a mixt. of a fibrinogen-contg. sample (275 **mg**/dl) and a reagent (III) contg. thrombin (100NIHU/ml and HEPES (RTM:buffer) (100mM; pH 7.35;) the vol. ratio sample (III) being from 1-2 (pref. 1:1.0-1.8). Salt (II) is 1 of :- NaCl (0.25-3.0 concn.), NaBr (0.1-1.0), NaI (0.1-0.4), KCl (0.25-1.5), KBr (0.1-1.0), KI (0.1-0.4), MgCl2 (0.04-0.25), CaCl2 (0.04-0.25). A pref. (III) contains 1.0-2.5M NaCl and 0.1-0.8M NaBr, and an esp. pref. reaction mixt. comprises 0.25-1.0M NaCl, 0.05-0.2 KF or NAF, 2-50 mM Na citrate and, as a discrepancy preventive (IV), 0.001-0.5 w/v% of a surfactant. Also claimed are reagents per se. These comprise salt a t high concn. (set at a level giving a **coagulation** time of 5-100 secs., measured under conditions as described above) and 20-500 NIHU/ml of thrombin or a protease. An esp. pref. reagent comprises 40-200 (NIHU/ml. thrombin, 30-200 ml. buffer (pH

7.0-8.0), 1.0-3.5M NaCl and 0.3-1.0 MNaBr. Alternatively, 2 reagents may be used, a first comprising (IV) and a second consisting of thrombin or a protease and (II) may be in the first or second reagent.

ADVANTAGE - The method uses undiluted samples of plasma, and conventional equipment for measurement of **coagulation** time. Samples having a low content of (I) can be assayed using a normal amt. of thrombin without use of expensive peptides or prolonging the **coagulation** time. The results correlate well with those obtd. by the conventional dilution method and can be used for routine blood tests.

Dwg.0/9

FS CPI EPI
FA AB; DCN
MC CPI: B04-B04D4; **B04-H19**; B04-L05C; **B05-A01A**; **B05-A01B**; B11-C08E; **B12-K04**; D05-A02C; **D05-H09**
EPI: S03-E14H

L186 ANSWER 12 OF 13 WPIX (C) 2002 THOMSON DERWENT
AN 1990-320268 [42] WPIX
DNN N1990-245413 DNC C1990-138692
TI Factor sensitive reagent for testing blood **coagulation** - contg. ellagic acid or its salts, **divalent** metal ion and cephalin.
DC B04 D16 S03
IN PROKSCH, G J
PA (PROK-I) PROKSCH G J
CYC 31
PI WO 9011368 A 19901004 (199042)*
RW: AT BE CH DE DK ES FR GB IT LU NL OA SE
W: AU BB BG BR CA FI HU JP KR LK MC MG MW NO RO SD SU
AU 9053502 A 19901022 (199104)
US 5055412 A 19911008 (199143)
ADT US 5055412 A US 1989-326381 19890321
PRAI US 1989-326381 19890321
REP 1.Jnl.Ref; DE 2915310; US 3486981; US 4732860
IC **C12Q001-56**; **G01N033-86**
AB WO 9011368 A UPAB: 19930928
A stable factor sensitive reagent for measuring partial thromboplastin time is claimed comprising (a) ellagic acid or its salts, (b) a **divalent** metal ion present at a molar ratio of 3-30 based on the ellagic acid or salt and (c) a cephalin.

The **divalent** metal ion may be e.g. **Mg**, Ca, Cu, Co, Fe, Pb, Mn, Sr or Zn ion. The cephalin is pref. soybean cephalin.

Also claimed is a stable reagent capable of forming a **procoagulation** reagent upon exposure to a source fo cephalin comprising (a) ellagic acid or its salts and (b) a **divalent** metal ion present at a molar ratio of 3 or less, but greater than 0.1 based on the ellagic acid or salt. The pH of the reagents may be adjusted using a buffer, e.g. N-2-hydroxyethylpiperazine-N, 2-ethanesulphonic acid hemisodium salt (HEPES hemisodium salt).

USE/ADVANTAGE - The reagents have an extended shelf life, the ellagic acid remaining suspended longer, improving reliability. The reagents also have improved activity. By selecting the **divalent** metal ion used, the reagents selective for different **coagulation** factors are made, e.g. if **Mg2+** is used, the reagent becomes sensitive to the presence or absence of factors like Factor X and lupus **coagulation** inhibitor.

0/0

FS CPI EPI
FA AB; DCN
MC CPI: B04-B01B; **B04-B04D3**; **B05-A01B**; **B05-A03**; B05-B01P; B06-A03; B11-C08; **B12-K04A2**; D05-H12
EPI: S03-E09E; S03-E14H1
ABEQ US 5055412 A UPAB: 19930928

Reagent for the determination of partial thromboplastin time comprises ellagic acid or its salt (pref. the Na salt), (approx. 0.1 mmol/l); a **divalent** metal salt (pref. **Mg**, Ca, Cu, Co, Fe, Pb, Mn, Sr or Zn), at concns. such that the molar ratio of metal ion to ellagic acid or its salt is 3-30); and cephalin, (pref. soyabean cephalin).

USE - The prods. are stable reagents for measuring blood clotting ability.

L186 ANSWER 13 OF 13 WPIX (C) 2002 THOMSON DERWENT
AN **1986-190883** [30] WPIX
DNN **N1986-142654** DNC **C1986-082175**
TI Complement system activity determination - by photometrically following lysis of sensitised erythrocytes by citrated blood plasma in a buffer contg. **calcium** and **magnesium** ions.
DC B04 C03 S03
PA (BEHW) BEHRINGWERKE AG
CYC 16
PI EP 188008 A 19860723 (198630)* DE 13p
R: AT BE CH DE FR GB IT LI LU NL SE
DE 3501496 A 19860724 (198631)
JP 61169763 A 19860731 (198637)
NO 8600167 A 19860811 (198639)
ZA 8600354 A 19860721 (198640)
AU 8652517 A 19860724 (198642)
ES 8704268 A 19870601 (198726)
ADT EP 188008 A EP 1985-116671 19851231; DE 3501496 A DE 1985-3501496 19850118; JP 61169763 A JP 1986-6601 19860117; ZA 8600354 A ZA 1986-354 19860117; ES 8704268 A ES 1986-550932 19860116
PRAI DE 1985-3501496 19850118
REP 4.Jnl.Ref; A3...8705; EP 132537; EP 132556; No-SR.Pub; US 4130634; US 4492761
IC A61K039-00; G01N033-55
AB EP 188008 A UPAB: 19930922
In a new procedure for the determination of the activity of the complement system of human or other mammalian blood by photometrically following the lysis of sensitised erythrocytes in a buffer contg. **calcium** and **magnesium** ions, there is used as test material blood plasma to which citric acid or a salt thereof has been added as **anticoagulant**.

ADVANTAGE - Use of plasma avoids the occurrence of falsely pathological CH50 sometimes observed with serum (cf. Am. J. Med. Technol. (1982) 48, 743 and 749), and the procedure with citrated plasma is less complex than the serum complement method described in Z. Naturforschung 20b, 569-574 (1965).

0/1
FS CPI EPI
FA AB
MC CPI: B04-B04D1; **B04-B04D3**; B04-B04D4; **B05-A01B**; B10-C02; B11-C07B2; B12-H02; **B12-K04A**; C04-B04D1; **C04-B04D3**; C04-B04D4; **C05-A01B**; C10-C02; C11-C07B2; C12-H02; **C12-K04A**
EPI: S03-E14H1; S03-E14H4

=> d his

(FILE 'HCAPLUS' ENTERED AT 13:36:21 ON 11 DEC 2002)
DEL HIS

FILE 'REGISTRY' ENTERED AT 13:49:35 ON 11 DEC 2002
E CALCIUM/CN
L1 1 S E3
E CALCIUM, ION/CN

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L2              1 S E23
                  E MAGNESIUM/CN
L3              1 S E3
                  E MAGNESIUM, ION/CN
L4              1 S E17

     FILE 'HCAPLUS' ENTERED AT 13:51:34 ON 11 DEC 2002
L5         302953 S L1 OR L2
L6         258968 S CA2 OR (CALCIUM OR CA)(L)ION
L7         432250 S L5,L6
L8         168480 S L3 OR L4
L9         134977 S MG2 OR (MAGNESIUM OR MG)(L)ION
L10        261345 S L8 OR L9
L11        125930 S L7 AND L10

     FILE 'REGISTRY' ENTERED AT 13:52:30 ON 11 DEC 2002
               E PROTEIN C/CN

     FILE 'HCAPLUS' ENTERED AT 13:52:30 ON 11 DEC 2002

     FILE 'REGISTRY' ENTERED AT 13:52:35 ON 11 DEC 2002

     FILE 'HCAPLUS' ENTERED AT 13:52:35 ON 11 DEC 2002

     FILE 'REGISTRY' ENTERED AT 13:52:36 ON 11 DEC 2002

     FILE 'HCAPLUS' ENTERED AT 13:52:36 ON 11 DEC 2002

     FILE 'REGISTRY' ENTERED AT 13:52:37 ON 11 DEC 2002

     FILE 'HCAPLUS' ENTERED AT 13:52:37 ON 11 DEC 2002

     FILE 'REGISTRY' ENTERED AT 13:52:39 ON 11 DEC 2002

     FILE 'HCAPLUS' ENTERED AT 13:52:40 ON 11 DEC 2002

     FILE 'REGISTRY' ENTERED AT 13:52:42 ON 11 DEC 2002

     FILE 'HCAPLUS' ENTERED AT 13:52:42 ON 11 DEC 2002
               S E3

     FILE 'REGISTRY' ENTERED AT 13:52:49 ON 11 DEC 2002

     FILE 'HCAPLUS' ENTERED AT 13:52:49 ON 11 DEC 2002

     FILE 'REGISTRY' ENTERED AT 13:53:10 ON 11 DEC 2002
               E PROTEIN C/CN
L12             1 S E3
                  E HUMAN PROTEIN C/CN
                  E ACTIVATED PROTEIN C/CN
L13             1 S E3
L14             1 S E8

     FILE 'HCAPLUS' ENTERED AT 13:56:14 ON 11 DEC 2002
L15          1746 S L12
L16          9740 S PROTEIN C OR VITAMIN K DEPENDENT PROTIN C OR CEPROTEIN OR BLO
L17          1133 S L13 OR L14
L18          9778 S L15-L17
L19            43 S L18 AND L11
L20             3 S BLOOD ANALYSIS+NT/CT AND L19
L21             4 S BLOOD COAGULATION+NT/CT AND L19
                  E BLOOD COAGULATION/CT
                  E E3=ALL
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                E BLOOD COAGULATION/CT
                E E3+ALL
                E E16+ALL
L22          16 S E2+NT AND L19
L23          18 S L20-L22

     FILE 'REGISTRY' ENTERED AT 14:01:05 ON 11 DEC 2002
                E VENOM/CN

     FILE 'HCAPLUS' ENTERED AT 14:01:06 ON 11 DEC 2002
                E VENOM/CT
                E E7+ALL
L24         163 S E3+NT AND L11
                E SNAKE/CT
                E E3+ALL
L25          13 S E7,E6 AND L11
                E VIPER/CT
                E E29+ALL
L26           6 S E7+NT AND L11
                E E6+ALL
L27           8 S E6+NT AND L11
                E AGKISTRODON/CT
L28          15 S E2-E56 AND L11
                E E3+ALL
L29          10 S E6+NT AND L11
L30           1 S L24-L29 AND L18
L31           1 S L24-L29 AND L19-L23
L32           1 S L30,L31
                E BLOOD-COAGULATION FACTOR/CT
L33       20912 S E3-E24,E26-E30
                E E25+ALL
L34       27891 S E2+NT
                E E35+ALL
L35       15709 S E7+NT
                E E6+ALL
L36       15709 S E7+NT
L37       39208 S L33-L36
                E METALS/CT
L38         221 S E7
L39       16393 S METAL(L)DIVALEN?
L40          77 S L37 AND L38,L39
L41         355 S L37 AND L10
L42         264 S L7 AND L40,L41
                E CATION/CT
                E CATIONS/CT
L43        5583 S E5
L44       23191 S CATION(L)DIVALEN?
L45         152 S L43,L44 AND L37
L46          93 S L7 AND L45
L47         294 S L42,L46
L48          37 S L47 AND 9/SC,SX
L49          13 S L47 AND L24-L32
                SEL DN AN 2 3 11 12 13
L50           5 S L49 AND E1-E15
L51          34 S L48 NOT L49
L52           7 S L51 NOT 9/SC
L53          27 S L51 NOT L52
                SEL DN AN L53 1 3 4 8 9 11 13 16 26
L54           9 S E16-E42
L55          14 S L50,L54
L56          30 S L23,L55
                SEL DN AN 2 7 11 12 14 15 16 18 19 20 21 22 23 24 25 26
L57          14 S L56 NOT E43-E90
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ACT GITOMER050A/A

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L59	(	2)	SEA FILE=REGISTRY ABB=ON	PLU=ON	("MAGNESIUM, ION (MG1+)"/CN O
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L61	(	1)	SEA FILE=REGISTRY ABB=ON	PLU=ON	MAGNESIUM/CN
L62	(	1)	SEA FILE=REGISTRY ABB=ON	PLU=ON	"BLOOD-COAGULATION FACTOR IXA
L63	(	1)	SEA FILE=REGISTRY ABB=ON	PLU=ON	"BLOOD-COAGULATION FACTOR XIA
L64	(	1)	SEA FILE=REGISTRY ABB=ON	PLU=ON	"BLOOD-COAGULATION FACTOR XII
L65	(	1)	SEA FILE=REGISTRY ABB=ON	PLU=ON	"TISSUE FACTOR (BLOOD-COAGULA
L66	(	1)	SEA FILE=REGISTRY ABB=ON	PLU=ON	"BLOOD-COAGULATION FACTOR VII
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L68	(	1)	SEA FILE=REGISTRY ABB=ON	PLU=ON	"PROTEIN C"/CN
L69	(	1)	SEA FILE=REGISTRY ABB=ON	PLU=ON	"ACTIVATED PROTEIN C"/CN
L70	(	1)	SEA FILE=REGISTRY ABB=ON	PLU=ON	"BLOOD-COAGULATION FACTOR V"/
L71	(	1)	SEA FILE=REGISTRY ABB=ON	PLU=ON	"BLOOD-COAGULATION FACTOR VA"
L72	(	65)	SEA FILE=REGISTRY ABB=ON	PLU=ON	(GPRP)/SQEP
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L77	(	1)	SEA FILE=REGISTRY ABB=ON	PLU=ON	"BLOOD-COAGULATION FACTOR X"/
L78	(	1)	SEA FILE=REGISTRY ABB=ON	PLU=ON	PROTHROMBIN/CN
L79	(	1)	SEA FILE=REGISTRY ABB=ON	PLU=ON	THROMBIN/CN
L80	(	1)	SEA FILE=REGISTRY ABB=ON	PLU=ON	THROMBOMODULIN/CN
L81	(	1)	SEA FILE=REGISTRY ABB=ON	PLU=ON	"PROTEIN C ACTIVATOR"/CN
L82	(	13488)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L58
L83	(	296092)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L60
L84	(	258968)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	CA2 OR (CA OR CALCIUM)(L)ION
L85	(	436328)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	(L82 OR L83 OR L84)
L86	(	9917)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L59
L87	(	164242)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L61
L88	(	134977)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	MG2 OR (MG OR MAGNESIUM)(L)ION
L89	(	127612)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	(L86 OR L87 OR L88) AND L85
L90	(	43)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L89 AND PROTEIN C
L91	(	14)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L89 AND (L68 OR L69)
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L93	(	12)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L92 AND (L62 OR L63 OR L64 OR
L94	(	278)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L89 AND (L62 OR L63 OR L64 OR
L95	(	12)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	(L92 OR L93) AND L94
L96	(	6)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	(L92 OR L93 OR L95) AND (BIOCH
L97	(	1)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	(L92 OR L93 OR L95) AND (SNAKE
L98	(	112205)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	("BLOOD, ANALYSIS"/CT OR "BLOO
L99	(	930)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L89 AND L98
L100	(	12)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L99 AND L94
L101	(	3)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L99 AND (L92 OR L93 OR L95 OR
L102	(	4370)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	C REACT? PROTEIN
L103	(	15)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L102 AND L89
L104	(	63)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	(L103 OR L100 OR L101 OR L92 O
L105	(	22)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L104 AND L94
L106	(	128)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	("ROSEN B"/AU OR "ROSEN BERT S
L107	(	281)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	("HALL C"/AU OR "HALL C M"/AU)
L108	(	18)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	"HALL CHRIS"/AU
L109	(	12)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	("HALL CHRISTINA"/AU OR "HALL
L110	(	2)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	(L106 OR L107 OR L108 OR L109)
L111	(	1)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L110 NOT ADENOSINE/TI
L112	(	22)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	(L105 OR L111)
L113	(	10)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L112 AND 9/SC
L114	(	1)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L112 AND 9/SX
L115	(	11)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	(L113 OR L114)
L116	(	11)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L112 NOT L115
L117	(	1)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L116 AND ("1981:187155"/AN OR
L118	(	7)	SEA FILE=HCAPLUS ABB=ON	PLU=ON	L115 NOT ("111:20117"/AN OR "1

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L119          8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L117 OR L118)
               ---------
L120         17 S L57,L119 AND L5-L11,L15-L57,L119
L121         15 S L120 AND (CA OR CALCIUM OR CA2 OR MG OR MAGNESIUM OR MG2)
L122          8 S L120 AND DIVAL?
L123         17 S L121,L122

     FILE 'HCAPLUS' ENTERED AT 14:31:41 ON 11 DEC 2002

     FILE 'BIOSIS' ENTERED AT 14:31:55 ON 11 DEC 2002
                E ROSEN B/AU
L124        187 S E3,E17
L125          1 S E28
                E HALL C/AU
L126        445 S E3,E25
L127          8 S E90-E92
L128        139 S 150?/CC AND L124,L126,L127
L129          1 S L128 AND DIVAL?(L)(METAL OR CATION OR ION)
L130          7 S L128 AND L1-L4
L131          5 S ?COAGUL? AND L128
L132          1 S L131 AND L129,L130
L133          1 S L125,L132

     FILE 'WPIX' ENTERED AT 14:35:22 ON 11 DEC 2002
                E ROSEN B/AU
L134         31 S E3,E13
                E HALL C/AU
L135         73 S E3,E18,E19
L136        103 S L134,L135
L137        911 S L16
L138      37929 S ?COAGUL?
L139          1 S L136 AND L137,L138
L140        546 S C12Q001-56/IC,ICM,ICS
L141        757 S G01N033-86/IC,ICM,ICS
L142       1224 S (B04-H19 OR C04-H19)/MC
L143       1034 S (B04-B04D3 OR C04-B04D3)/MC
L144      57824 S A220/M0,M1,M2,M3,M4,M5,M6
L145      45942 S A212/M0,M1,M2,M3,M4,M5,M6
L146          1 S L136 AND L140,L141,L142,L143
L147          1 S L139,L146
L148       2619 S L137,L138,L140,L141,L142,L143 AND (L144 OR CA2 OR CALCIUM)
                E CALCIUM/DCN
                E E86+ALL
L149       1520 S E2
L150         91 S L137,L138,L140-L143 AND L149
L151       2620 S L148,L150
L152        725 S L151 AND (L145 OR MG2 OR MAGNESIUM OR MG)
                E MAGNESIUM/DCN
                E E56+ALL
L153       1175 S E2
L154         26 S L151 AND L153
L155        726 S L152,L154
L156         52 S L155 AND PROTEIN(L)C
L157         47 S L155 AND (B12-K04? OR C12-K04? OR D05-H09)/MC
L158         19 S L155 AND L141
L159         16 S L156,L157 AND L158
L160        125 S L155 AND (B05-A? OR C05-A?)/MC
L161          9 S L160 AND L141
L162        102 S L155 AND ?VALEN?
L163         15 S L162 AND L156-L159
L164          3 S L162 AND L161
L165         18 S L162 AND L160
L166         26 S L163-L165
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L167          9 S L166 AND G01N/IC,ICM,ICS
                SEL L166 1 4 DN AN
L168          2 S E1-E6
                SEL DN L167 1 7 8
L169          6 S L167 NOT E7-E12
L170          8 S L168,L169,L147
L171         76 S L156-L159,L161 NOT L166-L170
L172         76 S L171 AND (CA2 OR CALCIUM OR A220/M0,M1,M2,M3,M4,M5,M6)
L173         42 S L172 AND (MG2 OR MAGNESIUM OR A212/M0,M1,M2,M3,M4,M5,M6)
                SEL DN AN L173 1 16 19 32
L174          4 S E13-E23
                SEL DN AN L173 22
L175          1 S E24-E26
L176         13 S L170,L174,L175
L177        276 S L140 AND L141
L178         12 S L177 AND L155
L179          8 S L178 NOT L176
L180          4 S L176 AND L178
L181         13 S L176,L180 AND L134-L180
L182          7 S L181 AND (A212 AND A220)/M0,M1,M2,M3,M4,M5,M6
L183          3 S L177 AND (A212 AND A220)/M0,M1,M2,M3,M4,M5,M6
L184          7 S L182,L183
L185          6 S L181 NOT L184
L186         13 S L184,L185

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